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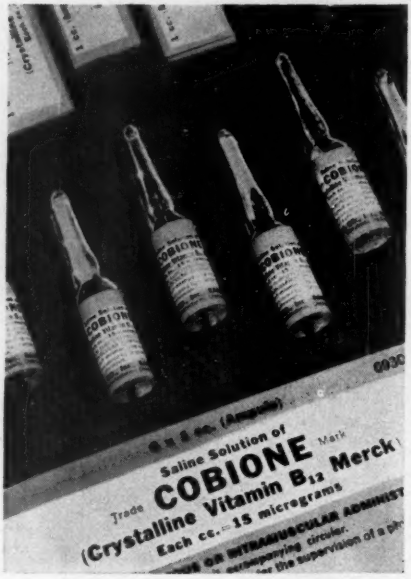

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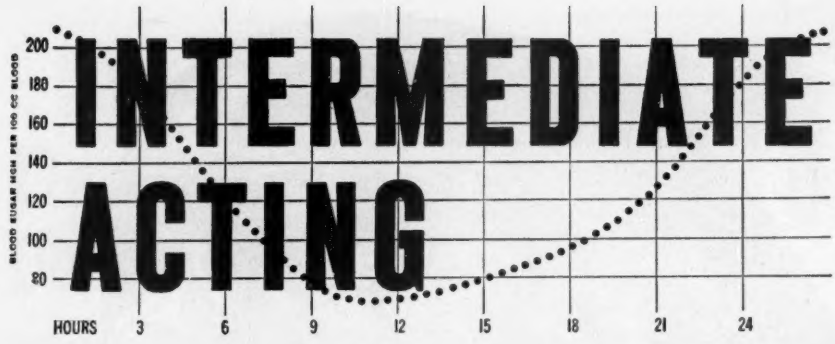

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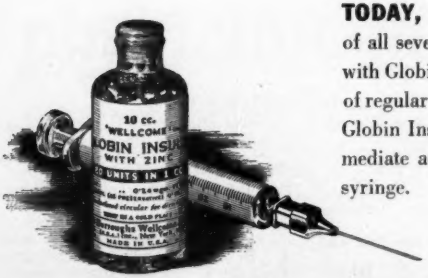

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948.

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*Joslin, E. P., Postgrad. Med.: 4:302 (Oct.) 1948.

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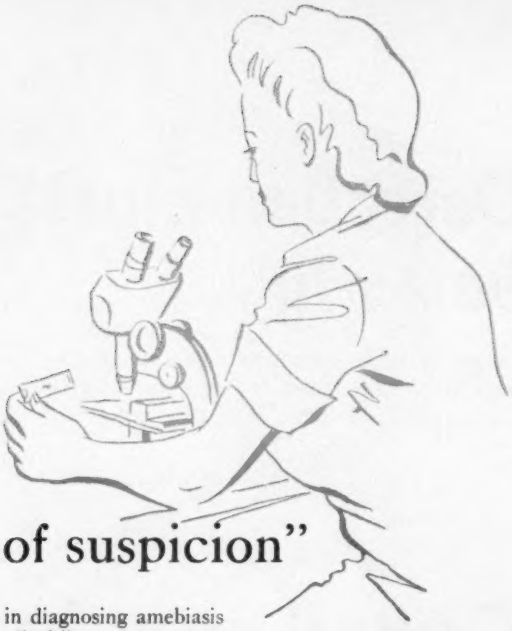

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1. Warshawsky, H.; Nolan, D. E., and Abramson, W.: Hepatic Complications of Amebiasis, New England J. Med. *235*:678 (Nov. 7) 1946.

2. Manson-Bahr, P.: Some Tropical Diseases in General Practice: "A Post-War Legacy," Glasgow M. J. *27*:123 (May) 1946.

ARCHIVES of INTERNAL MEDICINE

VOLUME 85 JANUARY 1950 NUMBER 1

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USE OF LITHIUM SALTS AS A SUBSTITUTE FOR SODIUM CHLORIDE

JOHN H. TALBOTT, M.D.

BUFFALO

MY INTEREST in lithium salts and independently in substitutes for sodium chloride dates back to the early 1930's, when the acid-base balance of patients with various metabolic disorders was under investigation. There were at least two aspects to this study. First, attention was centered on the sodium fraction [1] of body fluids. Since this ion accounts for approximately 90 per cent of inorganic base in serum and extracellular fluid, it was considered desirable in one phase of the investigation to maintain normal and sick persons on a diet as low in sodium chloride as possible, meanwhile making the food palatable on a constant dietary intake. A constant diet suitable for metabolic studies usually is monotonous, and when the content of sodium chloride is greatly reduced it becomes a difficult matter to accomplish the desired aim. A casual search was made for a satisfactory substitute to replace the salty taste of sodium chloride, and none was found that approached the palatability of sodium chloride added to food in the kitchen during its preparation or when used at the table. Ammonium chloride and potassium salts were of some value, but it was believed at that time that they did not aid materially in rendering a low sodium chloride diet palatable for most patients. Lithium salts were not considered, and therefore no experience was gained of their effect on patients maintained on a reduced sodium chloride intake.

The second interest concerned the specific use of lithium salts in the treatment of gouty arthritis.[2] The theoretic value of lithium salts in

From the Departments of Medicine, University of Buffalo School of Medicine and Buffalo General Hospital.

Read before the Section on Experimental Medicine and Therapeutics at the Ninety-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 9, 1949.

The researches of the laboratory in which these studies were made were supported in part by a grant from Mrs. Kathleen Stevens Chard, Cazenovia, N. Y., in memory of her mother, Mrs. Hattie Brooks Stevens, formerly of Buffalo.

1. Talbott, J. H., and Michelson, J.: Heat Cramps: A Clinical and Chemical Study, J. Clin. Investigation **12**:533 (May) 1933. Talbott, J. H.: Heat Cramps, Medicine **14**:323 (Sept.) 1935.

2. Talbott, J. H.; Jacobson, B. B., and Oberg, S. A.: The Electrolyte Balance in Acute Gout, J. Clin. Investigation **14**:411 (July) 1935.

gout was based on the enhancement in vitro of the solubility of urates following the addition of the lithium ion.[3] Daniels[4] used from 1 to 2 Gm. of lithium citrate daily as the recommended dose for gouty patients. The report by Cleaveland (1913)[5] was consulted, and it was noted that 4 to 8 Gm. of lithium chloride ingested in one day produced transitory weakness and mental symptoms. The dose of lithium carbonate was given by Biddle in "Materia Medica in Therapeutics" (1892)[6] as 0.7 to 2.0 Gm. per day. "The National Standard Dispensatory" (ed. 3, 1916)[7] lists a daily dose of 1.0 to 3.0 Gm. of the carbonate and an average daily dose of 2.6 to 4.0 Gm. of lithium salicylate.

At the conclusion of this review of past experience, it was believed proper to begin the experimental use of lithium salts for patients with gout. The trial was abandoned before many months because of the failure to note any specific increase in the urinary excretion of uric acid from the body of gouty persons, a decrease in the concentration of serum uric acid or any significant therapeutic benefit. These negative results were not reported. It is to be noted that the use of any of the lithium salts as a substitute for sodium chloride in the diet was not studied in either of these investigations.

In the intervening fifteen-odd years an increasingly large mass of evidence was accumulated which suggested that patients with cardiac failure or hypertension might benefit by a drastic reduction in the daily intake of sodium chloride. It was contended by a number of qualified clinical investigators that every effort should be made to achieve a low sodium chloride intake in order to reduce the work of the heart and kidneys. A satisfactory salt substitute for those patients who desired a salty taste to their food was obviously needed, lest the constitutional effects of inadequate nutrition offset the benefit of a low salt intake.

An ideal nontoxic taste substitute for sodium chloride should meet the following criteria:

1. It should be indistinguishable in taste from sodium chloride.
2. It should be nontoxic in quantities usually required.
3. It should be possible to add it to food at the table just as table salt is added.

---

3. Garrod, A. B.: A Treatise on Gout and Rheumatic Gout (Rheumatoid Arthritis), ed. 3, London, Longmans, Green & Co., 1876.

4. Daniels, A. L.: The Influence of Lithium and Atophan on the Uric Acid Excretion of a Gouty Patient, Arch. Int. Med. **13**:480 (March) 1914.

5. Cleaveland, S. A.: A Case of Poisoning by Lithium, Presenting Some New Features, J. A. M. A. **60**:722 (March 8) 1913.

6. Biddle, J. B.: Materia Medica and Therapeutics for Physicians and Students, ed. 12, Philadelphia, P. Blakiston's Son & Co., 1892.

7. Hare, H. A.: The National Standard Dispensatory, ed. 3, Philadelphia, Lea & Febiger, 1916.

4. It should not be destroyed in cooking if added to foods during preparation, nor should it be destroyed or partially decomposed if added to warm food at the table.

An aqueous solution of lithium chloride with citric acid and a trace of potassium iodide was offered to us for investigation and was found best to satisfy criterion 1. In fact, no other substance or combination of substances which was tried approached it as a palatable substitute for sodium chloride. The advantage of a clear and nonviscous solution as a salt substitute in contrast to dry crystalline matter was readily apparent. Patients could sprinkle a few droplets of the solution on sodium chloride–poor food, causing it to gain much in palatability, with an average total daily intake of lithium chloride not greater than 0.5 Gm.

Criterion 2 was next satisfied. The library investigation of 1933 was then repeated in regard to dosage and toxicity of lithium salts. Only three new papers had appeared, and no new conclusions were presented in the current textbooks of pharmacology. The effects of lithium on embryologic development in lower animals were investigated by Runnström [8] and reviewed by Needham.[9] MacLeod [10] discussed the possibility of lithium interfering with glucose metabolism in muscle and observed a reduction in motility of human spermatozoa in vitro suspended in Ringer's solution. As late as the twelfth edition of Cushny (1940) [11] no change from the edition of 1906 was made in the statements regarding lithium salts. McGuigan and others [12] in "Introduction to Materia Medica and Pharmacology" (1940) give the dose of lithium carbonate as 0.5 Gm. and that of lithium bromide as 1.0 Gm.

All the patients during the initial months of the study were in the hospital at the beginning of the period of use of the experimental preparation. With but few exceptions they were enthusiastic over the liquid substitute. No one found it unpalatable, and no one reported any symptoms of toxicity, though there was no restriction placed on the amount that could be used. During the first three months of this experimental period more than 50 patients were given the material; the period of use varied from a few days to the full three months. The subjects were instructed to use a sufficient quantity on their food to render it palatable.

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8. Runnström, J.: Analysis of the Effect of Lithium on Sea-Urchin Development, Biol. Bull. **68**:379, 1935.

9. Needham, J.: Biochemistry and Morphogenesis, London, Cambridge University Press, 1942.

10. MacLeod, J., in The Problem of Fertility, Proceedings of the Conference on Fertility, National Committee on Maternal Health, edited by E. T. Engle, Princeton, N. J., Princeton University Press, 1947.

11. Cushny, A. R.: Pharmacology and Therapeutics, ed. 12, revised by C. W. Edmunds and J. A. Gunn, Philadelphia, Lea & Febiger, 1940.

12. McGuigan, H. A.; McGuigan, R. A., and Krug, E. E.: An Introduction to Materia Medica and Pharmacology, St. Louis, C. V. Mosby Company, 1940.

so far as a salty taste was desirable. The average daily consumption of lithium chloride was approximately 0.5 Gm. per person per day in this group. The patients supplied with the experimental material were suffering from cardiac failure, hypertension or cirrhosis of the liver with ascites. A few patients preferred not to use this substitute after an initial trial period because they were not dependent on a salty taste for palatability of food and, consequently, for adequate nutrition. This group maintained that they could eat heartily enough on a low sodium chloride diet to obviate the need for a sodium chloride substitute. In only 3 cases did symptoms appear which were similar to those which have been reported recently as attributable to lithium. The symptoms were ascribed to one or more of the following factors: debilitating disease, low sodium intake, digitalization or the administration of mercurial diuretics. In no instance, however, were the symptoms of sufficient severity to attract any attention until after the use of lithium as a salt substitute became a matter of public discussion, though the patients were fully aware that they were receiving an experimental substance.

Simultaneously with the limited trial of unrestricted amounts, larger quantities were given to a few normal persons, as well as to hospital patients, in order to determine whether amounts varying from two to five times the average determined daily quantity for palatability would have any deleterious or demonstrable untoward effect. Six hospital patients and 4 normal persons were given quantities which varied from 2.0 to 5.0 Gm. of lithium chloride per day for periods of six to fourteen days. No symptoms were encountered during the period of ingestion except for some gastrointestinal distress which was attributed to the nonspecific effect of the salt on the gastrointestinal mucosa. The distress cleared rapidly after cessation of the ingestion of lithium chloride. The clinical trial was extended, and more than a dozen patients who used the lithium preparation on their food were followed for periods longer than six months. More than 50 patients who used it regularly were followed for more than three months. The unrestricted average daily intake of lithium chloride for these patients was not greater than 0.5 Gm.

Experiments with rats were also conducted. Ten rats were given 1 per cent of their body weight of a 0.05 per cent solution of lithium chloride by gastric intubation, five days per week for eight weeks. This corresponded to 50 mg. of lithium chloride per kilogram of body weight, being the equivalent of a dose of 3.7 Gm. per day for a 70 Kg. human subject. A second series of 10 rats was given twice this amount for a similar period. No symptoms of toxicity were noted in either series. At the end of the experimental period autopsies were performed on the animals; no gross changes were visible. Organs from 7 of the animals selected by chance were studied microscopically. Organs of control rats were also studied microscopically. It was concluded that except for

evidence of pneumonitis, which was observed in the lungs of some of the controls as well as in the experimental rats, there were no histologic changes of significance.

On the basis of these observations the investigational and clinical study was continued in other cities in the eastern portion of the country. The solution of lithium chloride was received enthusiastically by physicians and patients alike because it satisfied the palate of those on a low chloride diet who desired a salty taste to the food. Finally, after more than six months of experimental trial in this clinic and a shorter period of trial in other clinics with no reported instance of either mild or severe toxicity, the substitute was made available to patients generally.

Further experimental studies on normal persons and hospital patients were undertaken some time after this but were not completed until after the withdrawal of lithium substitutes for salt from the market. Again quantities considerably greater than the average daily intake, as previously determined in the clinic, were used. A total of 14 normal persons ingested 1.56 Gm. of lithium carbonate daily. This quantity is equivalent to 1.87 Gm. of lithium chloride and is approximately four times the determined average daily intake per person. The experiments were continued for five to fourteen days. Blood samples were taken two or more times in each instance for determination of sodium and lithium concentration in the serum. In 6 subjects the lithium concentration was 0.5 milliequivalents per liter or less and in only 1 was it as high as 1.1 milliequivalents. The maximum lithium concentration ranged from 0.5 to 1.0 milliequivalents in the other subjects. Some gastrointestinal irritability was noted in 6; correlation was observed between this symptom and the elevated serum lithium. The distress subsided after cessation of the intake and was gone seventy-two hours after the last dose was administered. Three subjects experienced drowsiness. There were no symptoms reported at lithium levels below 0.7 milliequivalents. Determinations of serum sodium showed no inverse relationship with serum lithium concentration. In each instance some increase in serum sodium concentration was noted. Although this increase was as great as 7.0 milliequivalents (table 1), it is believed that the range of these observations was not greater than might be noted in persons on an ad libitum diet.

The hospital patients (table 2), 11 in number, were under treatment for a variety of conditions, which included diabetes mellitus cardiac decompensation and chronic nephritis. Their ages varied from 46 to 79. The patients received lithium carbonate tablets in quantities equivalent to 2.2 to 4.6 Gm. of lithium chloride daily. The longest period of forced ingestion in this series was nineteen days. The concentration of serum sodium and serum lithium was determined one or more times for correlation with any change in the clinical state.

Two patients complained of gastrointestinal irritability and 1 of depression, 1 of tremors, 1 of anorexia and tremors and 1 of gastrointestinal distress and tremors. In 4 of the 5 instances maximum serum lithium levels were 2.3 milliequivalents or higher, ranging up to 3.9 milliequivalents. Minimum serum sodium levels in these 5 patients

TABLE 1.—*Experimental Observation on Serum Electrolytes in a Normal Person During Intake of 1.56 Gm. Lithium Carbonate*

Experimental Day	Electrolyte Concentration, mEq./L.	
	Lithium	Sodium
1	0.20	137.5
7	0.45	141.0
14	0.70	144.5
21	0.40	136.5

TABLE 2.—*Experimental Observations on Serum Electrolytes in Hospital Patients During Lithium Intake*

Subject	Duration of Lithium Intake, Days	Total Intake of Lithium Carbonate, Gm.	Maximum Electrolyte Concentration, mEq./L.		Symptoms
			Lithium	Sodium	
1	7	27	3.6	134.5	Gastrointestinal distress
2	8	15	3.2	132.5	Depression
3	5	15	2.9	135.0	None
4	7	18	0.1	138.0	None
5	13	42	...	141.5	Gastrointestinal distress
6	15	55	1.2	131.0	Anorexia, tremors
7	5	15	2.3	127.0	Tremors
8	12	36	3.9	140.5	Gastrointestinal distress, tremors
9	19	57	2.4	134.0	None
10	3	9	1.9	137.5	None
11	14	42	1.7	130.5	None

ranged from 127.0 to 141.5 milliequivalents. In the sixth patient the maximum serum lithium level was 1.2 milliequivalents and the minimum serum sodium level was 131.0 milliequivalents. In all instances recovery was complete within five days after cessation of these large doses of the experimental substance. On the other hand, in another patient the serum lithium reached a maximum of 1.7 milliequivalents, while the serum sodium decreased from 142 to 130.5 milliequivalents. This patient was suffering from chronic glomerular nephritis and generalized anasarca. He was given 3.0 Gm. of lithium carbonate, equivalent to 3.7 Gm. of lithium chloride, for fourteen days (a total of 42 Gm. of lithium

carbonate, equivalent to 52.5 Gm. of lithium chloride). His body weight decreased from 187.5 pounds (85 Kg.) to 176.5 pounds (80 Kg.). No untoward reactions developed.

Near the conclusion of these studies, I was notified that a death alleged to be associated with excessive lithium intake had been reported to the manufacturers. I also learned that after a conference with the Federal Food and Drug Administration all lithium substitutes for salt had been withdrawn from the market and steps had been taken to recall outstanding stocks. One manufacturer immediately mailed a letter to all physicians notifying them of this step and of the reported possibility of untoward effects. Ten days after the withdrawal from the market the

TABLE 3.—*Experimental Observations on Serum Electrolytes in Patients Alleged to Have Lithium Intoxication*

Patient	Age, Years	Serum Electrolyte Concentration, mEq./L.			Comment
		Lithium	Sodium	Potassium	
1	..	0.4	134.0	...	
2	52	1.4	110.0	...	Cardiovascular-renal disease
		0.6	118.5	6.4	Observations made 5 days later
3	76	0.4	149.5	5.6	Cardiovascular-renal disease
4	67	0.2	136.0	...	Hypertensive coronary disease
5	..	0.9	140.0	...	Hypertension
6	..	0.7	132.0	...	Malignant hypertension
7	19	1.9	137.0	...	Rheumatic heart disease
8	42	0.5	133.0	6.8	Hypertension
		0.5	134.0	5.3	
9	46	0.5	138.0	5.3	Hypertension, generalized arteriosclerosis
		0.5	134.0	5.0	

report of several deaths, alleged to have been caused by lithium poisoning, was broadcast. No advance notice of this broadcast, in order that physicians could prepare the several thousands of patients taking these salt substitutes for the alarming statements, was given the physicians, druggists or manufacturers by those responsible for the dissemination of the report. The prescribing physician was embarrassed in many instances by a deluge of telephone calls from his patients requesting advice, and the only information available was that reported over the air and in the newspapers. It is believed that the situation was not so serious as one was led to believe from the lay reports.

During the following days, a great number of physicians sought additional information, many times to obtain guidance in discussing the situation with patients and a few times to report cases of possible poisoning. In each instance of the latter situation a request was made to the attending physician for a sample of blood for determination of the lithium level in the serum. Blood from 9 patients was submitted for

analysis (table 3). In only 2 instances was the concentration of lithium greater than 0.7 milliequivalents; these values were 1.4 and 1.9 milliequivalents, respectively. It will be recalled that in the study of normal subjects untoward symptoms were observed only when the serum lithium was above 0.7 milliequivalents. Moreover, in the hospital patients I observed serum lithium concentrations as high as 2.9 milliequivalents without the appearance of untoward effects, and except in 1 case I did not observe signs of intoxication until serum lithium levels reached 2.3 milliequivalents.

Moreover, in the case of 2 of the 3 patients who showed the highest serum lithium levels it was noted that a low serum sodium level was also present. The patient with a serum lithium concentration of 1.4 milliequivalents had a serum sodium level of 119.0 milliequivalents, and the one with a serum lithium concentration of 0.7 milliequivalents had a serum sodium level of 132.0 milliequivalents; yet, a third patient with a serum lithium concentration of 1.9 milliequivalents had a serum sodium level of 137.0 milliequivalents.

The incidence of valid reactions due to the ingestion of lithium is unknown. Following the indiscriminate press and radio publicity an attempt was made in this clinic and others to contact hundreds of lithium users in order to obtain more precise information. The alarm had so frightened the majority of those who used the substitute that many symptoms, regardless of cause, were attributed to the ingestion of lithium. I myself have seen several patients claiming lithium intoxication whose symptoms, on close inquiry, were found to be due to other causes.

Reports of lithium intoxication which have appeared recently in the literature have been associated with the intake of surprisingly large amounts of lithium chloride. Patient 1 of the report of Hanlon and his associates [13] consumed 13 Gm. of lithium chloride in three days. This is at least eight times the average amount of lithium chloride found by my patients to satisfy their palate. Their second patient was given 43 Gm. of lithium chloride in sixteen days. This is approximately five times the average amount used by my patients. From the text of the paper by Corcoran and others [14] one gathers the impression that their first 2 patients also consumed large quantities of lithium chloride. It was impossible to ascribe the reported deaths to the ingestion of lithium since there were other complicating factors, each of which could have been responsible for the death of critically ill persons.

13. Hanlon, L. W.; Romaine, M., III; Gilroy, F. J., and Deitrick, J. E.: Lithium Chloride as a Substitute for Sodium Chloride in the Diet; Observations on Its Toxicity, J. A. M. A. **139**:688 (March 12) 1949.

14. Corcoran, A. C.; Taylor, R. D., and Page, I. H.: Lithium Poisoning from the Use of Salt Substitutes, J. A. M. A. **139**:685 (March 12) 1949.

Previous to the withdrawal of lithium substitutes for salt from the market toxic reactions had not been reported from the several clinics for cardiac and hypertensive diseases in which they had been evaluated over a period of many months. In retrospect, it is believed that the failure to observe any instance of intoxication was related in part to the fact that the sodium chloride content of the food eaten was probably higher than in some clinics where meticulous attention was given to a diet as nearly sodium chloride–free as possible. In this clinic and in several others a low sodium chloride intake is urged but extreme measures are not recommended in order to achieve this. The role that a low sodium regimen [15] or the administration of mercurial diuretics [16] may play in the development of the syndrome which has been attributed to lithium intoxication has not been established. Soloff and Zatuchni [17] recently reviewed the subject of the low sodium diet and enumerated several symptoms or physical findings that may appear independent of the intake of any salt substitute. These are as follows: weakness, lassitude, anorexia, nausea, emesis, restlessness, thirst not relieved with water, apathy, mental confusion, a fall in the blood pressure, an increase in the pulse rate, shock and coma. Furthermore, they maintain that any one of these conditions ". . . may be due to other causes, such as excessive sedation, digitalis, unrelated infection, thromboembolic phenomena or natural progression of the cardiac disease." Russek and Zohman [16] pointed out that "Regardless of the method of administration [of a mercurial diuretic] . . . severe diuresis occasionally causes weakness, anorexia, mental confusion, apathy, restlessness, delirium, hallucinations and more rarely coma and death." Thus many of the individual symptoms that have been attributed to lithium intoxication may, in a cardiac or hypertensive patient, appear quite independently of the intake of lithium. Likewise several of these symptoms may be induced in normal persons on a rigidly low sodium intake [15] without resorting to the administration of mercurial diuretics or other agents to enhance the excretion of sodium from the body.

If the concentration of serum sodium is low, as it was in several of the patients with alleged lithium intoxication (table 3), restoration of the serum sodium toward normal without altering the lithium intake and without alleviating the untoward symptoms offers the only convincing evidence of cause and effect. A series of patients studied with this

15. McCance, R. A.: Experimental Sodium Chloride Deficiency in Man, Proc. Roy. Soc., London s.B **119**:245 (Feb. 1) 1936.

16. Russek, H. I., and Zohman, B. L.: Cerebral Thrombosis Precipitated by Injection of a Mercurial Diuretic, J. A. M. A. **139**:922 (April 2) 1949.

17. Soloff, L. A., and Zatuchni, J.: Syndrome of Salt Depletion Induced by a Regimen of Sodium Restriction and Sodium Diuresis, J. A. M. A. **139**:1136 (April) 1949.

combination of experimental procedures has not been reported at the time of writing. What is probably likelier to be carried out is the discontinuance of the lithium intake and the increasing of the sodium intake. Under these conditions it is impossible to evaluate the role of lithium.

It has been mentioned that there may be a significant replacement of sodium in the blood and the extracellular fluid by lithium that has been ingested. For this reason the administration of sodium chloride has been suggested in the treatment of alleged lithium intoxication. There is no evidence from the data presented in this communication to substantiate this assumption of replacement. In the normal person (table 1) no reciprocal relationship was noted between the concentrations of serum sodium and of serum lithium. It will be recalled that there was no decrease in serum sodium in normal persons during the experimental intake of lithium. In hospital patients there was a decrease in serum sodium but the decrease was frequently several times the concentration of serum lithium. If a replacement of base occurs similar to the replacement of chloride following ingestion of the bromides it should be approximate in regard to quantity; such was not observed in this study. It is believed that any benefit that followed the treatment of apparent lithium intoxication with sodium chloride was related to the restoration of the serum sodium concentration in the body and to the correction of the deprivation of sodium.

SUMMARY

A historical review of the use of lithium chloride as a taste substitute for sodium chloride is presented.

Animal and experimental studies made prior to the introduction of lithium chloride as a salt substitute to physicians are recorded.

Untoward reactions following the use of lithium were not found in these clinical studies except in association with serum lithium concentrations above 1.0 milliequivalents.

Sodium chloride deficiency per se or other factors, such as the presence of a debilitating disease, the administration of mercurial diuretics or digitalization, may be associated with many of the symptoms which have been attributed to lithium intoxication.

100 High Street.

RENAL OSTEODYSTROPHY ASSOCIATED WITH DIABETES MELLITUS

Congenital Polycystic Hypoplasia of the Kidneys and Polycystic Disease of the Pancreas

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RECENTLY we had the opportunity to study an unusual case of chronic renal failure, associated with changes in bone suggestive of osteitis fibrosa cystica. The patient had true diabetes mellitus rather than renal glycosuria, which has been described in previous cases. Additional unusual findings at postmortem examination, including polycystic disease of the pancreas, prompted us to present this case with a review of the literature.

The triad of chronic nephritis, bony changes in the skeleton and physical dwarfism has been designated as renal rickets.[1] This is actually a misnomer in that the bony changes are not those characteristic of rickets and it is not even necessary that rickets be associated with this syndrome,[2] although it is sometimes associated with rickets.[3] A better term would be renal hyperparathyroidism with osteoporosis, as designated

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1. (*a*) Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1945, chap. 59, pp. 707-719. (*b*) Cantarow, A., and Trumper, M.: Clinical Biochemistry, ed. 3, Philadelphia, W. B. Saunders Company, 1945, pp. 172-173. (*c*) Grollman, A.: Essentials of Endocrinology, Philadelphia, J. B. Lippincott Company, 1941, p. 285.

2. (*a*) Albright, F.: The Parathyroids—Physiology and Therapeutics, J. A. M. A. **117**:527 (Aug. 16) 1941. (*b*) Albright, F.; Drake, T. G., and Sulkowitz, H. W.; Renal Osteitis Fibrosa Cystica, Bull. Johns Hopkins Hosp. **60**:377, 1937.

3. Pappenheimer, A. M., and Wilens, S. L.: Enlargement of the Parathyroid Glands in Renal Disease, Am. J. Path. **11**:73, 1935.

by Park and Eliot,[4] renal osteitis fibrosa cystica (Albright and others [5]) or osteodystrophy (Norman and others [6]). The last is the one adopted by the "Standard Nomenclature of Disease" of the American Medical Association.

In 1883, Lukas [7] first described patients with well proportioned dwarfism with bony changes similar to those in rickets, but which developed at a later age, and with impairment of renal function due to chronic interstitial nephritis. They showed increased nonprotein nitrogen, increased serum phosphorus and decreased blood calcium, and the disease was called renal rickets. The association of chronic nephritis and bony changes with variable blood chemistry findings has been reported frequently, but the total number of reported cases is still only around 100.

The condition usually starts in childhood during the period of skeletal growth, and most of the patients die in childhood [8]; however, a few cases have been reported in adults. The etiologic factor in the disease may be congenital defect or infection or a combination of the two.[9] Generally the cause is unknown and the physician sees the patient when the renal deficiency has reached a high degree. Chronic glomerulonephritis with destruction of most of the glomeruli, scarlet fever, congenital polycystic disease of the kidneys and congenital valves of the urethra or strictures of the ureter have been reported as the etiologic factor.[10]

4. Park, E. A., and Eliot, M. M., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1948, vol. 3, chap. 29, pp. 1-18.

5. (*a*) Albright, F.; Baird, P. C.; Cope, O., and Bloomberg, E.: Studies on the Physiology of the Parathyroid Glands: IV. Renal Complications of Hyperparathyroids, Am. J. M. Sc. **187**:49, 1934. (*b*) Albright, F.; Consolazio, W. V.; Combs, F. S.; Sulkowitz, H. W., and Talbott, J. H.: Metabolic Studies and Therapy in a Case of Nephrocalcinosis with Rickets and Dwarfism, Bull. Johns Hopkins Hosp. **66**:7, 1940.

6. Norman, J. S.; Perlman, R., and Bastable, S.: Renal Osteodystrophy, J. A. M. A. **133**:771 (March 15) 1947.

7. Lucas, cited by Fanconi.[15b]

8. Mitchell, A. G.: Nephrosclerosis (Chronic Interstitial Nephritis) in Childhood, with Special Reference to Renal Rickets, Am. J. Dis. Child. **40**:101 (July) 1930.

9. (*a*) Berg, M., Renal Rickets, Urol. & Cutan. Rev. **47**:676, 1943. (*b*) Greene, C. H.: Bilateral Hypoplastic Cystic Kidneys, Am. J. Dis. Child. **24**:1 (July) 1922. (*c*) Howard, T. L.: Renal Rickets or Renal Dwarfism, Am. J. Surg. **40**:323, 1938.

10. (*a*) Park and Eliot.[4] (*b*) Greene.[9b] (*c*) Bass, M., and Pakter, J., Congenital Polycystic Kidneys with Secondary Bone Changes (Renal Hyperparathyroidism; Renal Rickets), J. Mt. Sinai Hosp. **4**:882, 1938. (*d*) Bell, E. T.: Renal Diseases, Philadelphia, Lea & Febiger, 1946, pp. 68-70. (*e*) Parsons, L. G.: Bone Changes Occurring in Renal and Coeliac Infantilism and Their Relationship to Renal Rickets, Arch. Dis. Childhood **2**:7, 1927. (*f*) Rule, C., and Grollman, A.: Osteo-Nephropathy: A Clinical Consideration of "Renal Rickets," Ann. Int. Med. **20**:63, 1944.

In practically all patients the kidneys are found to be small, granular and sclerotic. There are the following signs of severe renal insufficiency: polyuria; low, fixed specific gravity; albuminuria; reduced phenolsulfonphthalein excretion, and elevated nonprotein nitrogen. The urine may contain leukocytes and bacteria as evidence of infection. Casts usually are not found. The chronic and severe renal condition with impairment of excretion leads to retention of phosphates with accumulation in the blood and excretion through the intestinal mucosa. The increased concentration of phosphates in the intestines interferes with absorption of calcium by the formation of insoluble calcium phosphates. This leads to reduced calcium concentration and usually to a high phosphorus content of the blood.[11] However, the blood calcium and phosphorus vary considerably, even in the same patient on different occasions. They may be high, low or normal at times. Park and Eliot [4] stated the belief that the variable calcium-phosphorus ratio is due to the impairment of renal function. They stated that in renal osteodystrophy the parathyroid activity is influenced by the inability of the kidneys to excrete phosphate and that therefore the high inorganic phosphorus level in the blood forces a decrease in the calcium level. With less renal damage and better excretion of the phosphates there is a lower blood phosphorus level and a higher blood calcium level. The phosphatase activity is also found to be increased.

The correlation between the metabolism of calcium and the parathyroid gland is well known, and changes in the parathyroid glands are to be expected in patients with renal osteodystrophy. In fact, secondary hyperparathyroidism has been reported in almost all cases.[12] The mechanism is unknown. Park and Eliot stated that the function of the parathyroid glands is to regulate the calcium-phosphorus ratio and to cause an equilibrium between these two elements. In tetany when the parathyroid glands have been removed the calcium level falls and the phosphorus level rises. When parathyroid is injected there is phosphate diuresis with a fall in the plasma phosphorus level and a rise in the calcium level. In a poorly functioning kidney the elimination of phosphates is impaired and there is a rise of the blood phosphorus level. The parathyroid glands try to maintain or reestablish the calcium-phosphorus ratio by increasing the calcium level, with an increase in the parathyroid secretion and consequent parathyroid hypertrophy.

11. Best and Taylor.[1a] Cantarow and Trumper.[1b] Mitchell.[8] Parsons.[10e] McFarland, D.: Experimental Phosphate Nephritis in Rat, J. Path. & Bact. **52**:17, 1941. Price, N. L., and Davie, T. B.: Renal Rickets, Brit. J. Surg. **24**:548, 1937.

12. Grollman.[1c] Albright.[2a] Pappenheimer and Wilens.[3] Albright and others.[5] Rule and Grollman.[10f]

These authors stated the opinion that the diseased kidneys oppose the parathyroid function, which the parathyroid glands try to overcome by increased activity.

The overactivity of the parathyroid glands causes bony changes. Here again, the exact mechanism is unknown. Greenwald and Gross [13] stated the opinion that the parathyroid hormone unites with the ionized calcium of the blood plasma to form an undissociated compound and that compensatory calcium is liberated from the bones. Thomson and Collip [13] stated that the parathyroid hormone acts directly and primarily on the bones. It does appear possible, as Albright and his associates stated,[2b] that the low blood calcium level stimulates the parathyroid glands and that the phosphorus level is elevated only secondarily because of the impaired excretion of the kidneys. These authors also assumed that the intermediate action of the parathyroid glands is not necessary to produce the bony changes. The acidosis alone, which is usually found in renal osteodystrophy, is sufficient to produce the bony changes. Cantarow and Trumper [1b] stated that the bony changes depend on the acidosis and on the inadequate absorption of calcium resulting from the excretion of large amounts of phosphorus into the intestines, forming insoluble calcium phosphates with consequent impairment of the absorption of calcium. Cooke and his co-workers [14] stated that the decalcification is due to the fact that phosphorus esters to keep up the normal rate of deposition of bone are lacking.

The bony changes show a varied picture with predominating osteoporosis. They resemble those found in hyperparathyroidism and depend on the age at which the condition develops. When the disease occurs in children the endochondrial changes are great, with thickening and deformity of the proliferating cartilage of the long bones, because of mechanical stress and strain in the absence of adequate deposition of lime salt. In adults there is absorption of bone with osteoporosis, formation of cysts, secondary fibrosis and proliferation of connective tissue. The disease may or may not be accompanied with rickets. Pappenheimer and Wilens [8] showed in their experiments that rickets and osteoporosis may be found together. In these patients, signs such as Harrison's groove, pigeon breast and rachitic rosary are present.[10e] Albright and others [2b] described a case in which no features of rickets were present. Park and Eliot [4] stated that rickets was not an essential part in this entity and that the essential part was osteitis fibrosa cystica. Renal dwarfism is manifested by a below normal, well proportioned stature.

13. Cited by Cantarow and Trumper.[1b]

14. Cooke, W. T.; Barclay, J. A.; Govan, A. D. T., and Nagley, L.: Osteoporosis Associated with Low Serum Phosphorus and Renal Glycosuria, Arch. Int. Med. 80:147 (Aug.) 1947.

DeToni and Fanconi [15] first published a case of renal osteodystrophy associated with renal diabetes. Only a few more cases have been published [16] since their original description. All the reports have concerned children under 5 years, and there has been a marked familial and hereditary tendency. All the patients showed osteoporosis, a low calcium level, a low inorganic phosphorus level in the blood, hypochloremia, glycosuria and acidosis. The glycosuria appeared to be of the renal type because the blood sugar level was low or normal. The majority of these patients died before the age of 7, with the terminal picture of uremia.

Cook and others [14] reported the case of a 39 year old white man with a serum sodium chloride content of 600 mg., a calcium content of 10.3 mg. and a phosphorus content of 2.2 mg., per hundred cubic centimeters; the alkaline phosphatase level was 16.6 units; there was glycosuria with an almost normal blood sugar level and marked progressive osteoporosis. Autopsy showed only a defect of the renal tubules. The authors concluded that their case supported Hunter's hypothesis that osteoporosis may occasionally be unassociated with signs of chronic nephritis. Cases of this type are characterized by defect of the renal tubules, osteoporosis with or without fractures, a normal calcium and a low serum phosphorus content, a normal blood sugar level and renal glycosuria. Similar cases involving adults have been reported in the literature under the name of Milkman's syndrome, after the original description by Milkman.[17] These cases are characterized by low blood calcium and blood phosphorus levels, glycosuria with a low blood sugar level and osteoporosis with multiple fractures and diffuse nephritis.

Patients with cystine storage disease (Bürki [18] and Lignac [19]) show renal damage, dwarfism, bony changes and cystine in the urine or deposition of cystine crystals in the cornea and conjunctiva.

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15. (*a*) de Toni, G.: Remarks on Relation Between Renal Rickets, (Renal Dwarfism) and Renal Diabetes, Acta pædiat. **16**:479, 1933. (*b*) Fanconi, G.: Nephrotic Glycosuric Dwarfism with Hypophosphatamic Rickets, Jahrb. f. Kinderh. **147**:299, 1936; (*c*) Non-diabetic Glycosuria and Hyperglycosuria in Older Children, ibid. **133**:257, 1931.

16. McCune, D. J.; Mason, H., and Clarke, H. T.: Late Rickets with Glycosuric and Inorganic Acid Acidosis (Fanconi Type), Am. J. Dis. Child. **58**:673 (Sept.) 1939; Intractable Hypophosphatamic Rickets with Renal Glycosuria and Acidosis (Fanconi Syndrome), ibid. **65**:81 (Jan.) 1943.

17. Edeiken, L., and Schneeberg, N. G.: Multiple Spontaneous Idiopathic Symmetrical Fractures: Milkman's Syndrome, J. A. M. A. **122**:865 (July 24) 1943. Milkman, L. A.: Pseudofractures, Am. J. Roentgenol. **24**:29, 1930.

18. Bürki, E.: Cystine Disease in Renal Dwarfism in Children, with Special Reference to Ocular Findings, Ophthalmologica **101**:257, 1941.

19. Lignac, G. O. E.: Syndrome Consisting of Affections of the Kidney, Stunted Growth, Rickets and Disturbed Cystine Metabolism, Am. J. M. Sc. **196**:542, 1938.

Finally, osteoporosis due to primary hyperparathyroidism must be considered. It is well established that primary hyperparathyroidism due to adenoma or hyperplasia of the glands may in turn produce chronic renal disease. The differential diagnosis of primary and secondary hyperparathyroidism is usually easy. A high blood calcium and a low inorganic phosphorus level are specific in primary hyperparathyroidism. Diffuse nephrocalcinosis and renal stones can be demonstrated. Microscopically, primary hyperplasia of the parathyroid glands is associated with large, water-clear (*wasserhelle*) cells, whereas the glands in secondary hyperparathyroidism show chief cells.[20] Bony changes precede those in the kidneys.

An excellent classification of renal osteodystrophy was given by Rule and Grollman.[10b] They divided renal "osteo-nephropathy" into the following types:

An Etiological Classification of Osteo-Nephropathy

A. Due to primary urinary tract disturbances

1. Chronic glomerulonephritis, pyelonephritis, nephrosis
2. Congenital malformations: Polycystic kidneys, renal hypogenesis
3. Urinary tract obstruction with secondary renal lesions: Urethral valves; prostatic enlargement; calculi; strictures of urethra, bladder neck or ureter; hydro-ureter
4. Primary tubular functional changes which may or may not show anatomical changes.
   a. Hypochloremic-glycosuric type (de Toni-Fanconi syndrome)
   b. Hyperchloremic type without glycosuria

B. Due to primary extra-renal disturbances

1. Endocrine disease
   Hyperparathyroidism (osteitis fibrosa cystica)
2. Metabolic disturbance
   Cystine storage disease.

The blood chemistry findings were summarized by Rule and Grollman as follows: The osteonephropathies due to urinary disturbances are associated with a normal or slightly reduced blood calcium and an elevated blood phosphorus level, an elevated nonprotein nitrogen level, normal or slightly reduced carbon dioxide–combining power, normal serum chloride levels, pronounced anemia and the absence of glycosuria. The patient with the glycosuric type has a reduced serum calcium and blood phosphorus level, a normal or slightly elevated nonprotein nitrogen level, reduced carbon dioxide–combining power, glycosuria and ketonuria. The hyperchloremic type of patient shows a reduced serum calcium and blood phosphorus level, a normal or slightly elevated nonprotein nitrogen

20. Rogers, H. M.; Keating, F. R., Jr.; Morlock, C. G., and Barker, N. W.: Primary Hypertrophy and Hyperplasia of the Parathyroid Glands Associated with Duodenal Ulcer, Arch. Int. Med. **79**:307 (March) 1947.

level, reduced carbon dioxide–combining power, elevated serum chloride levels and no glycosuria. The patient with primary hyperparathyroidism shows an elevated serum calcium level, reduced blood phosphate levels, a normal nonprotein nitrogen level, normal carbon dioxide–combining power, normal chloride levels and no glycosuria.

REPORT OF CASE

This case does not fit exactly in any of the aforementioned etiologic groups. There was no familial tendency, the blood sugar level was elevated, the blood nonprotein nitrogen and serum phosphorus levels were elevated and, finally, the patient reached adulthood.

A white man of 25 years was admitted to the hospital on July 30, 1947 complaining of pains involving the lower portion of the back, both knees, both hips and occasionally the shoulders. He had been in the Army from Oct. 16, 1942 to Oct. 10, 1945, and had been overseas in Italy on combat duty. He had been given a point discharge.

Prior to military service he had had occasional pain in the lower portion of the back, but the pain had become aggravated while he was in the service. Prior to and occasionally after induction he had had fainting spells with loss of consciousness of short duration. He stated that during these attacks he had had fever, dizziness and faintness which occasionally led to unconsciousness. He knew of the presence of convulsions only from reports of witnesses who had been present during the attacks. Prior to admission, the pains in the joints had all become more severe. He complained of chronic weakness and lassitude. He stated that he had had "weak kidneys" all his life. By this, he meant that he had had enuresis up to the age of 12 years and even later had had frequency, nocturia and bed wetting. There was no history of hematuria, renal infection, renal calculi, scarlet fever or frequent sore throats, and there was no family history of renal disease.

Physical Examination.—This revealed a chronically ill, poorly developed and poorly nourished white man. The weight was 108 pounds (49.0 Kg.); the height, 5 feet 3½ inches (161 cm.), and the intelligence quotient, 85. The temperature was normal. The blood pressure was 125 systolic and 60 diastolic. The teeth were in very poor condition, with evidence of advanced pyorrhea. The chest showed evidence of rickets, with a definite Harrison groove and rachitic rosary. The heart was enlarged 1 cm. to the left of the midclavicular line. There was a soft systolic murmur, heard best over the apex of the heart. The liver extended 2 fingerbreaths below the right costal margin, and slight ascites was present. Movement of the joints was not limited, but there was some pain in the left knee joint and in both hips. There was tenderness of the left knee but no crepitation. There was a cystic mass about 4 cm. in diameter and 2 cm. high in the region of the left acromioclavicular joint, which was fluctuant. There was a similar mass in the back in the region of the lumbar portion of the spine. There was severe clubbing of the fingers, probably representing fractures of the decalcified terminal phalanges.

Roentgenologic Examination.—Roentgenograms of the long bones, the cervical, thoracic and lumbar portions of the spine, the pelvis, the thorax, the abdomen, the teeth and the skull were made. There was considerable cortical thickening, woolly appearance of trabecular structures and multiple tiny cysts in the cortical portion of the long bones. The pelvis and vertebrae showed moderate osteoporosis. The bones of the calvarium as well as the mandibles showed diffuse osteoporosis (fig.

1). The sella turcica was normal. The teeth showed loss of the normal periodontal membrane. The shoulders showed an absence of the distal 2.5 cm. of each clavicle (fig. 2). The terminal phalanges of the fingers showed erosion of the bone with marked destructive changes. A flat plate of the abdomen showed the kidneys to be greatly diminished in size, and an intravenous pyelogram showed no evidence of dye in either kidney. A retrograde pyelogram showed the renal outline to be greatly decreased in size.

Laboratory Examination.—On admission there was a nonprotein nitrogen level of 117 mg., a uric acid level of 13.3 mg., a serum calcium level of 11.7 mg. and an

Fig. 1.—Roentgenogram of the skull made on Aug. 12, 1947, showing diffuse osteoporosis.

inorganic serum phosphorus level of 3.9 mg., per hundred cubic centimeters. Urinalysis revealed albumin (1 plus) and sugar (1 plus).

Course.—A few days after admission the patient went into coma and had clonic and tonic convulsions. He was treated with fluids intravenously, the administration of oxygen and supportive measures, and in a few days he was fully conscious. Numerous laboratory tests were performed during his stay in the hospital. The values for nonprotein nitrogen, uric acid, creatinine, urea, serum calcium, serum phosphate, carbon dioxide-combining power, cholesterol, sodium chloride, serum phosphatase and glucose are given in the table. Blood counts persistently showed between 3,000,000 and 3,500,000 red blood cells, hemoglobin 60 per cent to 70

per cent and a normal white blood cell and differential count. The sedimentation rate was constantly elevated between 90 and 110 mm. in one hour. The blood pressure varied from 125 to 135 systolic and from 60 to 70 diastolic. Several blood cultures were negative. Hepatic function tests showed an icteric index of 4, a cephalin flocculation reaction of 2 plus and thymol turbidity of 7.5 units. Excretion of phenolsulfonphthalein on August 15 was 0.2 per cent; on October 24, it was 16 per cent. Concentration and dilution tests showed that the specific gravity did not go higher than 1.008 or lower than 1.005. Results of the glucose tolerance test were as follows: fasting, 185 mg.; one-half hour, 311 mg.; one hour, 320 mg.;

Fig. 2.—Roentgenogram of the left shoulder region made on August 17, showing amorphous deposits in the region of the acromioclavicular joint and absence of the distal 2.5 mm. of the clavicle. The neck and the upper portions of the shaft of the humerus show oval, elongated areas of rarefaction, which are cystic in appearance.

two hours, 238 mg., and three hours, 320 mg., per hundred cubic centimeters. Urea clearance was 8.4 per cent of normal; the first specimen was only 6.4 per cent of normal. Numerous urinalyses showed values for albumin from a trace to 1 plus and values for sugar from negative to 3 plus. Fractional urinalysis showed sugar (2 to 3 plus) in the second and third portion. There was no acetone at any time. The results of the Sulkowitch calcium test of the urine were positive, from a trace to 1 plus. The reaction for urobilinogen was positive in the 1:50 dilution. Bence-Jones protein was never found. The urine culture was negative. The bone marrow was normal. The cyst of the left shoulder was aspirated, and

30 cc. of what appeared to be pus was removed. Examination of this fluid showed no organism on direct smear or culture. The diabetes was easily controlled with diet and the administration of 20 units of insulin.

In an attempt to lower the inorganic blood phosphorus level, the patient was given aluminum hydroxide in the hope that this would combine with the phosphorus and be eliminated. In an attempt to arrest the decalcification of the bones, vitamin D and calcium gluconate were given. Milk was not given because of its phosphorus content.[21] This treatment was successful inasmuch as roentgenograms of the bones made in December showed pronounced improvement, with calcium deposition and with much less rarefaction and fewer osteodystrophic changes (fig. 3). There was a lowering of the serum phosphorus from 13.1 mg. per hundred cubic centimeter on August 7 to 2.04 mg. on November 5. The patient was feeling much better

Blood Chemistry Findings

Date	Non-protein Nitrogen, Mg./100 Cc.	Urea Nitrogen, Mg./100 Cc.	Uric Acid, Mg./100 Cc.	Creatinine, Mg./100 Cc.	Total Proteins, Mg./100 Cc.	Sodium Chloride Mg./100 Cc.	Cholesterol, Mg./100 Cc.	Carbon Dioxide-Combining Power, Vol. %	Calcium, Mg./100 Cc.	Phosphorus, Mg./100 Cc.	Phosphatase, Mg./100 Cc.	Glucose, Mg./100 Cc.
7/30/47	.....	.....	13.3	....	....	...	143	....	11.7	3.9	....	...
8/ 5	117	.....	18.7	....	....	...	...	22.6	....	....	....	...
8/ 6	166.5	130	....	13.7	....	520	...	26.3	10.3	9.3	....	....
8/ 7	154.6	.....	23.1	16.6	6.6	390	147	30.0	10	13.1	7.7	120
8/ 9	127	....	....	12.0	....	...	...	44.9	....	....	....	195
8/11	78	.....	....	6.0	7.0	431	...	45.8	10.6	11.2	....	216
8/13	112.5	88	14.4	....	7.1	...	...	43	10.5	7.8	2.6	163
8/18	135.5	93.7	12.9	9.2	7.6	410	147	36.5	10.5	8.0	7.2	202
8/25	154.5	97	13	7.1	7.4	452	141	40.3	10.0	8.4	8.4	136
8/30	118.3	125	15	6.9	7.2	430	100	43.9	11.2	6.3	8.1	168
9/24	100	63	6.7	5.0	....	...	...	....	....	....	....	91
9/29	134	.....	....	....	....	...	...	....	10.9	5.4	12.6	94
10/ 6	138.3	.....	8.7	....	....	...	...	....	....	4.8	....	230
10/13	148.5	98	11.0	....	....	...	...	....	10.9	5.2	....	160
10/29	135	124	13	9.4	....	...	187	....	13.5	4.6	11.2	183
11/ 5	150	112.5	13.5	9.6	....	...	210	....	10	2.04	7.8	177
11/21	160	110	8.7	11.7	....	...	108	....	15.3	....	6.0	140
12/ 3	183	150	13.5	14.3	....	...	92	....	14.7	3.8	....	175
12/ 8	179.6	111	8.1	11.0	....	...	170	....	15.8	3.5	....	130
12/ 9	136.6	.....	....	7.0	....	...	...	....	14.6	2.8	....	...
1/ 5/48	138.5	.....	....	....	....	...	...	....	12.4	3.9	5.4	270
2/16	222	.....	....	....	....	...	...	....	11	7	....	180
3/ 1	214	141.5	8.4	5.9	....	420	259	....	14	6.0	4.8	176
3/ 8	250	200	7.7	8.7	....	440	...	46.7	10.7	6.5	5.1	258

and insisted on going on a three weeks' pass. In March of 1948 his condition became worse. He complained of dyspnea, lassitude, increased weakness and loss of appetite. He died March 20, with a picture of terminal uremia.

Necropsy.—At the postmortem examination the body was found to be that of a poorly nourished, poorly developed white man, measuring 5 feet 3½ inches in length and weighing approximately 100 pounds (45.4 Kg.) There was a flaring of the costal angle from the xiphoid process, and firm nodules were present at each costochondral junction. Cystlike masses comprised the distal third of each clavicle. These cysts each measured about 7 cm. in diameter and were filled with a thick, yellow fluid. Smears of this fluid revealed much crystalline material but no

21. (*a*) Parsons.[10e] (*b*) Fanconi.[15b] (*c*) Anderson, D. H.: Cystic Fibrosis of the Pancreas, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1948, vol. 1, chap. 29A, pp. 1-20. (*d*) Graham, G., and Oakley, W. G.: Treatment of Renal Rickets, Arch. Dis. Childhood **13**:1, 1938.

organisms or growth; however, the body had been arterially embalmed prior to autopsy. The distal ends of the terminal phalanges of the hands were nodular and soft. All these bones cut easily. When the abdomen was opened, about 750 cc. of brown ascitic fluid was found.

The heart weighed 460 Gm. Near the aortic orifice in the interventricular septum an area of cardiac muscle with a mottled, yellow appearance was observed. A calcific nodule in the sinus of Valsalva was found just inferior to the orifice of the right coronary artery. There were calcified arteriosclerotic plaques in the proximal portion of the thoracic aorta.

Fig. 3.—Roentgenogram of the skull made on Jan. 8, 1948, showing less osteoporosis and better calcification of the skull.

The right lung weighed 860 Gm. and the left 740 Gm. There were adhesions between the lower lobe of the right lung and the anterior chest wall and the diaphragm. The lower lobes of both lungs were increased in consistency. The bronchi and the cut surfaces of these lobes freely exuded a red, thin fluid.

The liver weighed 1,340 Gm. The cut surface revealed several small foci of grayish yellow material, which appeared caseous.

The pancreas was spherical in shape and very firm. It occupied the duodenal curve, but there was no pancreatic tissue found in the region usually occupied by the tail of the pancreas. The cut surface revealed numerous cysts, approximately 4 to 5 mm. in diameter and grayish white in color.

The spleen weighed 340 Gm. Scattered over its surface were many grayish white, umbilicated lesions, 1 to 2 cm. in diameter. The spleen cut with increased

resistance. The cut surface revealed destruction of the normal gross architecture by numerous scattered, small, firm nodules, 0.5 to 1 cm. in diameter.

The kidneys were very small, weighing a total of 80 Gm. Each kidney measured 7 cm. in length. The capsules stripped with difficulty, tearing the parenchymal tissue and leaving a white, rough, hard subcapsular surface showing numerous cysts measuring 0.5 to 1 cm. in diameter. The kidneys cut with difficulty and with a gritty sensation. The cortical markings and the corticomedullary junction could not be identified grossly. The cut surface also contained small cysts similar to those on the surface (fig. 4).

Lymph nodes removed from the celiac plexus and the right pulmonary hilus were approximately 1 cm. in diameter and were firm. The cut surface revealed what appeared to be abscesses.

The four parathyroid glands were each enlarged to 2 cm. in diameter and were firm in consistency. The cut surface revealed the capsule to be thin. The parenchymal tissue appeared homogeneous; it was yellow-gray in color.

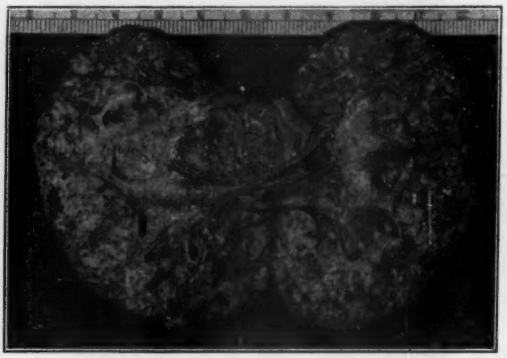

Fig. 4.—Gross photograph of the right kidney made on March 22, showing the small size, the destruction of the usual architecture by interstitial calcification and a few of the multiple small cysts which were visible grossly. The left kidney was similar.

Histopathologic Examination.—The heart revealed many hypertrophied fibers with large rectangular nuclei. There was increased intercellular stroma in the interventricular septum. About some of the smaller cardiac vessels infiltration of lymphocytic and mononuclear cells was encountered. About the calcific deposit in the sinus of Valsalva multinucleated giant cells were encountered. Mild coronary atherosclerosis was also seen.

The lungs showed pulmonary edema and congestion of the pulmonary vessels with thickening of the alveolar walls. There were many macrophages containing brown pigment granules in the alveoli. Many of these were multinucleated. There were other multinucleated cells about some of the bronchi. These were located in the submucosal area, and some were found about blue-gray laminated concretions.

Sections of the liver showed several abscesses containing a central core of polymorphonuclear and degenerated cells surrounded by a dense layer of fibrous tissue. This fibrous tissue contained lymphocytes, monocytes, plasma cells, multi-

nucleated giant cells, degenerating liver cells and degenerating bile ducts. The surrounding hepatic tissue showed compression of the liver columns. In many other periportal spaces there were infiltrations of plasma cells and lymphocytes with an accompanying increase in fibrous tissue. Many of the liver cells showed vacuolation.

The pancreas presented a pronounced increase in fibrous tissue throughout, with numerous cysts lined with a single layer of cuboid epithelial cells (fig. 5). These cysts were surrounded by dense fibrous tissue, in some instances containing only pancreatic ducts. There were varying degrees of degeneration of the parenchymal cells.

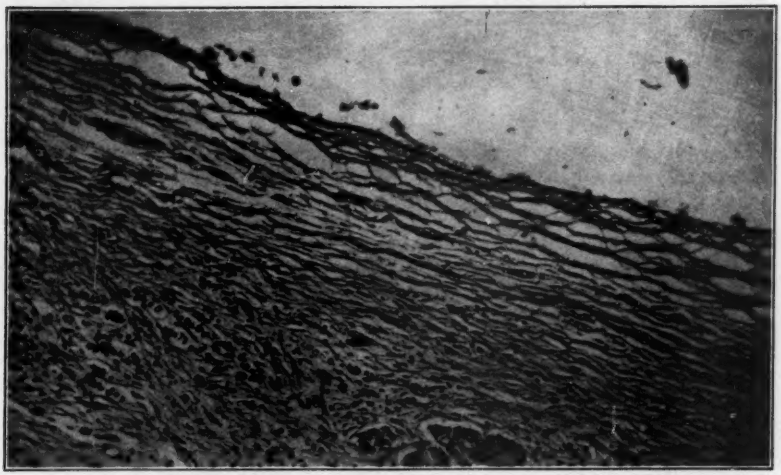

Fig. 5.—Low power photomicrograph of the wall of a pancreatic cyst, showing the cuboid lining surrounded by fibrous tissue with only a small amount of acinar tissue remaining.

In the spleen numerous granulomatous lesions were encountered which showed central caseous necrosis surrounded by whorls of fibrous tissue and multinucleated giant cells. These nodules were found in groups. We were unable to demonstrate acid-fast bacilli in these lesions.

In the kidneys numerous cysts of varying size were observed. They were lined with a single layer of flat epithelial cells. In a few of these cysts small, degenerated glomerular tufts could be demonstrated (fig. 6 *A*). There were few glomeruli seen; these were rather large, and the glomerular capillaries were dilated and much congested. Many of the tubules were dilated; in many instances they seemed to make up part of the cyst walls. Most of the remaining tubules were surrounded by a thick collar of calcification; this calcification was greatest about the proximal tubules (fig. 6 *B*). Many of the tubules showed evidence of degeneration, and many contained purple-staining casts.

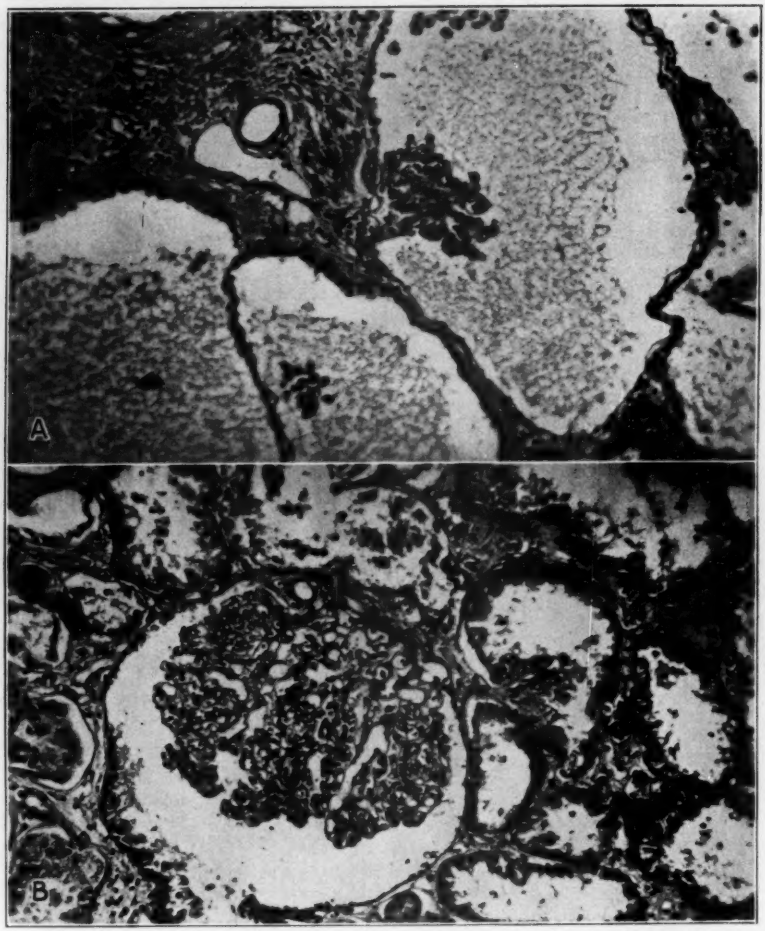

Fig. 6.—*A*, low power photomicrograph of a kidney showing the small glomerular tuft in one of the cystic spaces. *B*, low power photomicrograph of the kidney showing one of the few large glomeruli and the marked interstitial collar of calcification about the proximal convoluted tubules.

The celiac and pulmonary hilar lymph nodes showed minute abscesses, with masses of polymorphonuclear cells surrounded by fibrosis. These foci had largely destroyed the normal histologic arthitecture of the nodes.

The bone sections showed an increased amount of fibrous tissue between the bony spicules, with many clasmatocytes accumulated in these areas. Particularly was this true in the sections taken from the region of the clavicular cysts.

The parathyroid sections showed striking hyperplasia of the chief cells, which were arranged either in acinar groups or in solid sheets (fig. 7). One area showed hemorrhage into the gland with accompanying phagocytosis of blood pigment. Another localized area revealed compact group of cells containing many red, homogenous, cytoplasmic granules of varying size.

Anatomic Diagnosis.—This included the following: congenital polycystic hypoplasia of the kidneys; congenital polycystic disease of the pancreas; hypertrophy

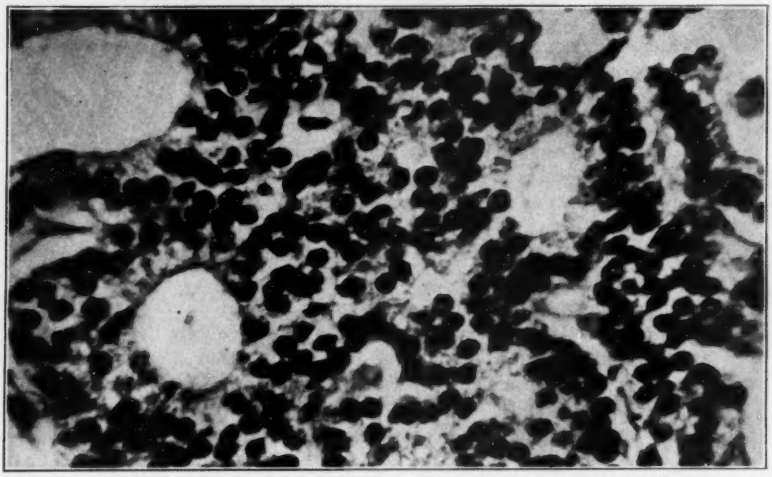

Fig. 7.—High power photomicrograph of the hyperplastic parathyroid tissue.

and hyperplasia of the parathyroid glands; osteitis fibrosa cystica (secondary); diabetes mellitus; granulomatous abscesses of the spleen; abscesses of the liver and the lymph nodes; mild coronary atherosclerosis and arteriosclerosis; myocardial hypertrophy, and pulmonary edema and congestion.

COMMENT

Dr. E. T. Bell,[22] of the University of Minnesota, reviewed the slides in this case and suggested the diagnosis of congenital polycystic hypoplasia of the kidneys. He had discussed this type of lesion under the heading of bilateral renal hypoplasia.[10d] He reported 1 of his own cases, that of an infant of 14 months, and referred to a patient who died at 3½

22. Bell, E. T.: Personal communication to the authors.

years, as reported by Greene. Most of the reported cases involved children who were stillborn or died shortly after birth. We have not found a report of this type of lesion in an adult. We believe this congenital polycystic hypoplasia of the kidney to represent the primary pathologic factor in this case.

The hypertrophy and hyperplasia of the parathyroid glands were probably secondary to chronic renal insufficiency. The interstitial calcification of the kidneys, the generalized bony decalcification with the formation of cysts and the arteriosclerotic processes noted in the aorta and the coronary arteries were probably the result of a combination of hyperparathyroid activity and chronic renal insufficiency, with its accompanying acidosis and retention of phosphorus.

Congenital polycystic disease of the pancreas accompanying polycystic disease of the kidney has been described; so we feel that this too represents a primary lesion.

We think the diabetes mellitus in this patient was an additional disease entity, related to the renal osteodystrophy only in that it may possibly have resulted from the widespread fibrosis in the pancreas. Most reports of cases of fibrocystic disease of the pancreas stress the loss of exocrine function rather than of endocrine function.[21c] However, Norris and Tyson [23] reported the number of islets of Langerhans as "definitely less than . . . normal," and Wigglesworth [24] stated that they were "thought to be decreased in several cases."

It is our opinion, as well as that of Dr. E. T. Bell and Dr. F. C. Helwig,[25] that the granulomatous lesions in the spleen were the result of a tuberculous infection, despite our inability to demonstrate acid-fast organisms. The cause of the abscesses in the liver and the lymph nodes was not demonstrated. All cultures were negative. We were unable to demonstrate any organisms by Gram's or Giemsa's method or with acid-fast stains. We do not know the significance of the red intracytoplasmic granules found in some of the parathyroid sections.

SUMMARY

A case of renal osteodystrophy in an adult with chronic azotemia and diabetes mellitus is presented with the autopsy findings, and the literature is reviewed. The unusual findings of bilateral hypoplastic polycystic disease of the kidneys and polycystic disease of the pancreas are discussed. So far as we have been able to determine, no similar case has been reported in the literature, although cases with renal glycosuria have been recorded.

23. Norris, R. F., and Tyson, R. M., The Pathogenesis of Polycystic Pancreas: Reconstruction of Cystic Elements in One Case, Am. J. Path. **23**:485, 1947.

24. Wigglesworth, F. W.: Fibrocystic Disease of the Pancreas, Am. J. M. Sc. **212**:351, 1946.

25. Helwig, F. C.: Personal communication to the authors.

USE OF PARAAMINOBENZOIC ACID IN DERMATOMYOSITIS AND SCLERODERMA

Report of Six Cases

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THE PURPOSE of this report is to present certain preliminary observations on the effects of paraaminobenzoic acid in dermatomyositis and in scleroderma. Neither the cause nor the pathogenesis of these rare conditions is understood. The concept of "diffuse collagen disease," however, is generally accepted as being applicable to them and to lupus erythematosus. Baehr and Pollack [1] have pointed out that this does not necessarily indicate a close relationship between these disorders, and that it cannot be assumed that their pathogeneses are similar. Nevertheless, it appeared logical to anticipate from the results obtained in lupus erythematosus [2] that paraaminobenzoic acid might also be beneficial in dermatomyositis and in scleroderma.

The rationale for administering large doses of paraaminobenzoic acid to patients with lupus erythematosus has been dealt with elsewhere.[2a,c] Briefly, it was recalled that exposure to sunlight may induce a relapse or cause an exacerbation of lupus erythematosus. It was also known that manifestations of sensitivity to sunlight have been encountered in persons receiving sulfonamide compounds. Since paraaminobenzoic acid and sulfonamide drugs are metabolite antagonists, it was reasoned that the former might possibly exert a beneficial effect in

From the Departments of Internal Medicine and of Dermatology and Syphilology, University Hospital.

1. Baehr, G., and Pollack, A. D.: Disseminated Lupus Erythematosus and Diffuse Scleroderma, J. A. M. A. **134**:1169 (Aug. 2) 1947.

2. (*a*) Zarafonetis, C. J. D.; Curtis, A. C., and Grekin, R. H.: The Effects of Para-Aminobenzoic Acid in Lupus Erythematosus: Preliminary Report, Univ. Hosp. Bull., Ann Arbor **13**:122, 1947. (*b*) Zarafonetis, C. J. D.: Recent Clinical Studies with Para-Aminobenzoic Acid; abstracted, Am. J. Med. **5**:625, 1948. (*c*) Zarafonetis, C. J. D.; Grekin, R. H., and Curtis, A. C.: Further Studies on the Treatment of Lupus Erythematosus with Sodium Para-Aminobenzoate, J. Invest. Dermat. **11**:359, 1948.

lupus erythematosus. Accordingly, a clinical trial was undertaken; the results obtained in 18 cases were recorded.[2c]

While the aforementioned study was under way, there arose an opportunity to treat a patient with dermatomyositis with paraaminobenzoic acid. The patient had observed that exposure to sunlight aggravated the discomfort of her cutaneous eruption. For the reasons given and because the patient was rapidly becoming worse despite empiric measures with other substances, it was deemed justifiable to try paraaminobenzoic acid. Details of the ensuing favorable progress of this patient are given in the case reports (case 1). Another patient was then treated, primarily for dermatomyositis. This subject, however, also exhibited prominent features of scleroderma which regressed during the period of therapy with paraaminobenzoic acid. Treatment of additional patients with scleroderma of course followed. The present report deals with the results observed in 1 case of classical dermatomyositis (case 1), 1 with mixed features of dermatomyositis and scleroderma (case 2) and 4 of scleroderma. Brief accounts of the findings and clinical courses for all 6 subjects who received paraaminobenzoic acid follow.[3]

REPORT OF CASES

CASE 1.—A. K., a 59 year old white housewife, was admitted to the University Hospital on Sept. 2, 1947, complaining of itching of the skin, weakness and inability to swallow solid foods. She had been well until February, when an erythematous, papular and pruritic rash developed over the cervical region. This gradually spread to involve the skin of the face, the upper portion of the thorax and the arms, and similar lesions appeared on the legs. Edema of the face was evident initially. The patient noted that exposure to sunlight caused increased itching of the involved areas of skin. As the cutaneous involvement progressed she became aware of increasing muscular weakness. Difficulty in swallowing was present in March and gradually became more pronounced. There had been a 32 pound (14.5 Kg.) loss of weight during the seven months of illness.

Physical Examination.—On admission the temperature was 100.4 F., the pulse rate 98 per minute, the respiration rate 22 per minute and the blood pressure 148 systolic and 78 diastolic. The patient appeared to be chronically ill. There was evidence of recent loss of weight. Examination revealed an erythematous eruption involving the skin of the entire back, the anterior aspect of the neck and the upper portion of the chest onto the breasts; a few patches were scattered on the anterior portion of the trunk. There were several palm-sized plaques on the inner aspect of the thighs, with smaller patches scattered over the outer surface of the thighs and on the legs. The arms were similarly involved, and there were plaques on the extensor surface of the hands, particularly over the metacarpophalangeal

3. Paraaminobenzoic acid was administered to these patients as sodium or potassium paraaminobenzoate. Solutions of these compounds were prepared from paraaminobenzoic acid which was supplied by Merck & Co., Rahway, N. J. Tablets of sodium paraaminobenzoic acid, 0.5 Gm. each, were contributed by Wyeth, Incorporated, Philadelphia, for use in these cases.

joints. There was moderate atrophy of the musculature of the shoulder girdle with associated weakness of marked degree. Slight enlargement of the cervical, axillary and inguinal lymph nodes was present. The liver was palpable 6 cm. below the right costal margin. The rest of the physical examination was noncontributory.

Laboratory Examination.—Laboratory findings included normal values for hemoglobin and white cells. Urinalysis showed numerous leukocytes per high power field and occasional coarse granular casts. The twenty-four hour urinary excretion of creatine was 878 mg. on September 3. Roentgen examination of the upper portions of the gastrointestinal tract and the chest was noncontributory. Biopsy of the right deltoid and right gastrocnemius muscle was performed on September 9. The pathologic diagnosis of dermatomyositis was made from microscopic examination of the specimen of deltoid muscle. There was variation in the size and staining of the muscle fibers, and there were numerous perivascular infiltrations of lymphocytes (fig. 1*A*). In the specimen of gastrocnemius muscle, however, there was noted only an occasional inflammatory infiltration.

Course and Treatment.—The patient was given sulfathiazole, 1 Gm. four times daily, and thyroid 16 mg. twice daily. This program of therapy was followed from September 4 to September 18. During this period low grade fever continued and the weakness and dysphagia progressed. The patient complained of nausea much of the time, and there was occasional vomiting. By the seventeenth hospital day her weight had declined 18 more pounds (8.2 Kg.). Weakness had become extreme, and the patient was unable to raise herself from the bed without assistance. Treatment was changed to administration of sodium paraaminobenzoate, 2 Gm. every two hours, beginning on September 18. A few doses were missed on the following day because of a gastrointestinal roentgen study. By September 20 the patient's appetite was greatly improved, she was able to eat and retain solid foods, there was some return of strength and the erythematous eruption had faded somewhat. Therapy with sodium paraaminobenzoate was maintained at 24 Gm. daily, with gradual subjective and objective improvement. The patient had gained sufficient strength to sit up for photographs by September 23 (fig. 2). With progressive alleviation of her symptoms the patient insisted on returning to her home; she was discharged on October 9. She was advised to continue therapy with sodium paraaminobenzoate, 24 Gm. daily, and to return in two weeks. She was seen again on October 22. Improvement in strength had continued, and the eruption had almost faded. There was considerable pigmentation in the previously infiltrated areas. The patient had taken the drug only during the daytime, averaging 12 to 14 Gm. daily. In view of the continued improvement on this reduced dosage it was suggested that she maintain the program and return every two weeks for check-up examinations.

A few days later she experienced a severe gastrointestinal upset after some dietary indiscretion. She was unable to take sodium paraaminobenzoate for a few days and then decided to omit therapy entirely. She was not observed at this time, but she later stated that in about a week the erythema began to reappear and that weakness returned rapidly. She therefore resumed therapy, taking 2 Gm. four times daily. On Jan. 9, 1948, it was learned that edema of the eyes and ankles had developed. The patient was advised to discontinue sodium paraaminobenzoate, to force fluids and to omit salt from her food. Within a few days the edema had subsided and treatment was resumed.

On February 22 the patient returned to Ann Arbor for presentation at the meeting of the Chicago Dermatological Society. She now was stronger and able

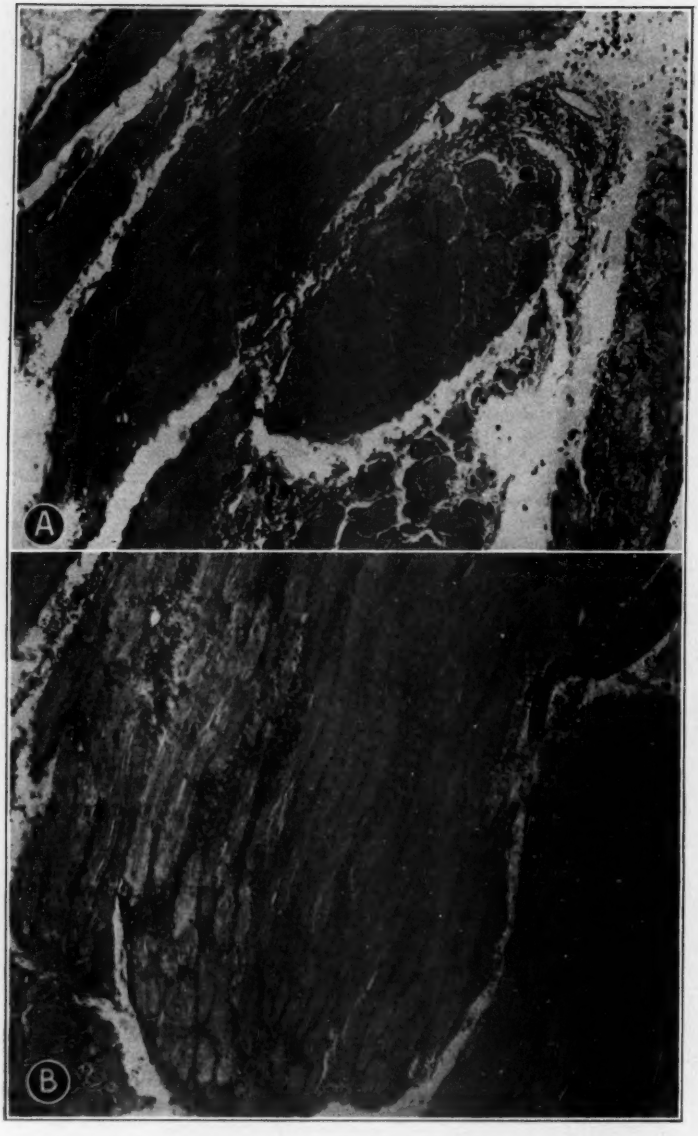

Fig. 1.—Photomicrographs of biopsy specimens from patient 1. *A*, specimen of right deltoid muscle taken on Sept. 9, 1947, ten days before beginning therapy with paraaminobenzoic acid. *B*, specimen taken from the same muscle on July 14, 1948, after ten months of medication with paraaminobenzoic acid.

to perform almost all her household duties. Examination revealed the skin to be lightly pigmented. Muscular atrophy was more evident in the right shoulder girdle than in the left. The hair was very thin, but the patient stated that it had ceased to fall out and that some regrowth was occurring. Although edema was not evident at that time, the medication was changed to alternate courses of three days each of potassium paraaminobenzoate and sodium paraaminobenzoate. The potassium salt was well tolerated, and after April 12 the patient continued on 6 to 8 Gm. daily of that compound alone. Gradual improvement continued. In July, however, a firm, 2.5 cm. mass was detected in the right breast. Radical

Fig. 2.—Photograph of patient 1 on Sept. 23, 1947, the fifth day of treatment (further data in text).

mastectomy was performed on July 14, and biopsy specimens were taken from the pectoralis major, pectoralis minor and deltoid muscles. The pathologic diagnosis of medullary and scirrhous carcinoma of the breast was made. Seven of ten lymph nodes examined showed metastases. The muscle findings were summarized by the pathologist as follows: "The small portion of deltoid muscle shows marked degenerative changes, including Zenker's necrosis. There is variation in the size and staining of muscle fibers with some fragmentation of sarcoplasm. Moderately heavy perivascular infiltrations of lymphocytes and monocytes are present between fibers of voluntary muscles. Angiomyositis is present" (fig. 1 *B*).

Convalescence was satisfactory and postoperative roentgen irradiation was administered. Meanwhile, the patient continued on a program of potassium para-aminobenzoate, 2 Gm. four or five times daily, which she was still following at the time of writing. The appearance of the patient on July 26, 1948, is shown in figure 3.

Fig. 3.—Photograph of patient 1 on July 26, 1948, twelve days after mastectomy.

CASE 2.—D. K., a 40 year old white man, had been well until February 1945, when he noted the onset of redness, pain and swelling of the right ankle. This subsided after a few days, but there was a more serious recurrence the following month. Subsequently both ankles and legs became involved and there were associated cutaneous changes. Generalized weakness, night sweats, daily fever and progressive loss of weight were present for the next three years. The patient was virtually bedridden for two years. During the course of his illness he was admitted to the University Hospital on several occasions. Extensive studies were per-

formed, and a variety of diagnoses were entertained. By February 1947 the diagnoses of dermatomyositis, gynecomastia and secondary anemia had been established. In view of the dramatic result achieved in case 1 with paraaminobenzoic acid, this subject was asked to return for a trial of similar therapy. Accordingly, he was readmitted to the University Hospital on Feb. 16, 1948.

Fig. 4.—Photographs of left hand of patient 2. *A*, on March 3, 1948, one week after the beginning of therapy with paraaminobenzoic acid; no change is apparent from the appearance before treatment. *B*, on April 2, 1948; improvement is evident after less than five weeks of treatment.

Physical Examination.—The patient appeared chronically ill and debilitated. The temperature was 100 F. The skin over the dorsum of the left hand was smooth, shiny, tightly bound down and reddish brown in color. Similar changes were present in the feet and legs, extending almost up to the knees. These changes severely limited movement of the affected parts. There were extensive

xanthomas on the eyelids and across the nose. In addition, numerous large, rounded areas of thickened skin bound to subcutaneous tissue were present on the hands, the forearms and the inner aspect of the thighs. The breasts were prominent, and glandular tissue was palpable in them. Results of the remainder of the physical examination were not remarkable.

Laboratory Examination.—The hemoglobin concentration was 10 Gm. per hundred cubic centimeters, with 3,300,000 red blood cells per cubic millimeter. The blood findings were otherwise normal. A twenty-four hour urine collection was found to contain 0.722 Gm. of creatine. The remaining studies were noncontributory.

Fig. 5.—Photographs of legs of patient 2: *A*, on Dec. 19, 1946; *B*, on July 16, 1948, after almost five months of therapy with paraaminobenzoic acid.

Course and Treatment.—Therapy with sodium paraaminobenzoate was begun on February 25. The initial dosage schedule was 3 Gm. every three hours (24 Gm. per day). At that time it was observed that the patient's left hand and wrist had become red and turgid with what was believed to be an acute exacerbation of the sclerodermatous process (fig. 4 *A*). By April 2 the patient was no longer febrile and the involvement of the left hand had subsided (fig. 4 *B*). The patient was discharged and continued therapy with sodium paraaminobenzoate, 15 to 18 Gm. daily, at home. Gradual and impressive improvement followed. The appetite returned, and the weight increased from 121 to 155 pounds (55 to 70 Kg.). The skin over the hands and legs became soft, moist and flexible (fig. 5). It is of additional interest that the xanthomas became reduced in size and the gynecomastia subsided. The nodular areas of induration on the inner aspect of the thighs and elsewhere regressed and were no longer palpable at the time of this report.

CASE 3.—H. J., a 43 year old white woman, was admitted to the University Hospital on April 12, 1948, with the chief complaint of "tight skin." Beginning in 1941 she had experienced progressive skin changes which began in the fingers and gradually spread to involve the entire body surface. Because of the thickening of the skin of the face chewing was difficult and solid foods had to be ground for her. The patient also had considerable epigastric distress, which was relieved by food and tums® (a proprietary antacid). There was no history of hematemesis or tarry stools. The past history revealed that the patient had undergone a "stomach operation for stricture" in 1938.

Physical Examination.—The patient appeared chronically ill and weak. The skin over the hands, forearms, face, neck, chest and abdomen was thick, indurated

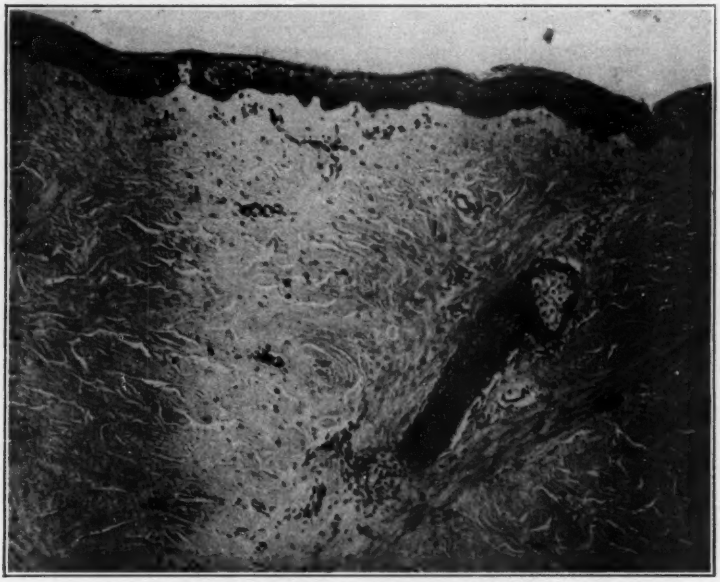

Fig. 6.—Photomicrograph of biopsy specimen of the skin of patient 3, taken on April 16, 1948. Characteristic changes of scleroderma are evident.

and adherent to the subcutaneous tissues. The skin of the lower extremities was also involved, but not so severely. The mouth could be opened only slightly, owing to the tightness of the skin of the face. There was pronounced limitation of motion of most of the joints. The fingers were almost motionless, and the elbows could be flexed only moderately. Movement of the shoulder joints was minimal, with the arms practically fixed to the wall of the chest. Examination of the chest and abdomen gave negative results.

Laboratory Examination.—The blood and urine were normal. Microscopic examination of the biopsy specimen from the skin revealed changes characteristic of scleroderma (fig. 6).

Course and Therapy.—On April 16 therapy with sodium paraaminobenzoate was begun, 2 Gm. every three hours. The drug was well tolerated, and within a few days the patient stated that her skin was beginning to feel less tight. Objectively, she appeared able to open her mouth wider and able to move her neck, fingers, and other involved areas through a slightly greater range. She was discharged on May 8, to continue therapy with paraaminobenzoic acid at home. She returned on May 20, very happy over the marked improvement which had ensued. She was able to eat normally, as the skin about the mouth was softened and relaxed. She was capable of more facial expression and could smile easily. The skin of the neck and the upper portion of the chest was softened and relaxed, so that the arms could be moved overhead and the patient could comb and brush her hair. Similarly, there was improvement in the hands and fingers (figs. 7 and 8). The patient was advised to continue therapy at home and to return in one month for reexamination and further evaluation of her course, but on the following day she was en route home by airplane and rough weather was encountered. This apparently precipitated nausea, severe vomiting and retching and then hematemesis. She was admitted to another hospital in shock and died one week later. Details of the terminal course are lacking.

Case 4.—M. O. M., a 38 year old housewife, was admitted to the University Hospital on March 2, 1948. The present illness had begun in mid-January, with soreness in the calves of the legs. Within a few weeks progressive weakness of the arms and legs was noted and a feeling of tightness developed in the skin of the limbs. By the time of admission the patient experienced difficulty in getting in and out of bed because of extreme weakness. Edema about the eyes and of the feet had been present for two weeks. The past history was negative except for the presence of eosinophilia of 30 per cent or greater for the preceding five years.

Physical Examination.—General examination gave normal results except for the findings in the extremities and the presence of edema about the eyes. The muscles of the arms and legs felt indurated and were tender to palpation, and the overlying skin was tense. Muscular strength was decreased generally; this was especially evident in the right biceps and triceps muscles. Pitting edema of the feet was present (2 plus). The neurologic examination was negative.

Laboratory Examination.—Laboratory findings included a hemoglobin value of 9.8 Gm. per hundred cubic centimeters, with 3,700,000 red blood cells per cubic millimeter. The white blood cells numbered 10,800, with 31 per cent eosinophils. The differential count was otherwise not remarkable. The urinary excretion of creatine was 890 mg. in twenty-four hours. Biopsy of the skin and the gastrocnemius muscle of the right leg revealed the following: There was hyperkeratosis of the epidermis with atrophy of the rete pegs and fragmentation of collagen. Perivascular infiltrations, including eosinophils, were present in the skin and voluntary muscle. Trichinas were not found. The pathologist interpreted the changes as compatible with a diagnosis of dermatomyositis.

Course and Treatment.—The clinical diagnosis was dermatomyositis or acute edematous scleroderma. Therapy with potassium paraaminobenzoate was instituted on March 7. The patient received 2 Gm. every three hours for four days; the drug was well tolerated. The patient was discharged on March 10 and was advised to take 3 Gm. of potassium paraaminobenzoate at three hour intervals for seven doses daily, omitting one dose in the night in order to obtain more rest. At the time of discharge the patient felt subjectively stronger and could get about more easily. The edema had diminished considerably.

Fig. 7.—Photographs of patient 3. *A*, on April 13, 1948, three days prior to the institution of therapy with paraaminobenzoic acid. *B*, on May 20, after slightly more than one month of treatment. Loosening of the skin is apparent, especially at the breast folds. *C*, on May 20; the patient was able to raise her arms overhead and to smile broadly.

The patient was readmitted on April 30. In the interim the potassium paraaminobenzoate had been taken without difficulty for two weeks; abdominal distention and nausea had then occurred. Medication was omitted for three days and then resumed at a dosage half that prescribed. The patient stated that there had been general improvement until the abdominal discomfort appeared and that some of the initial symptoms had returned after the dosage was reduced.

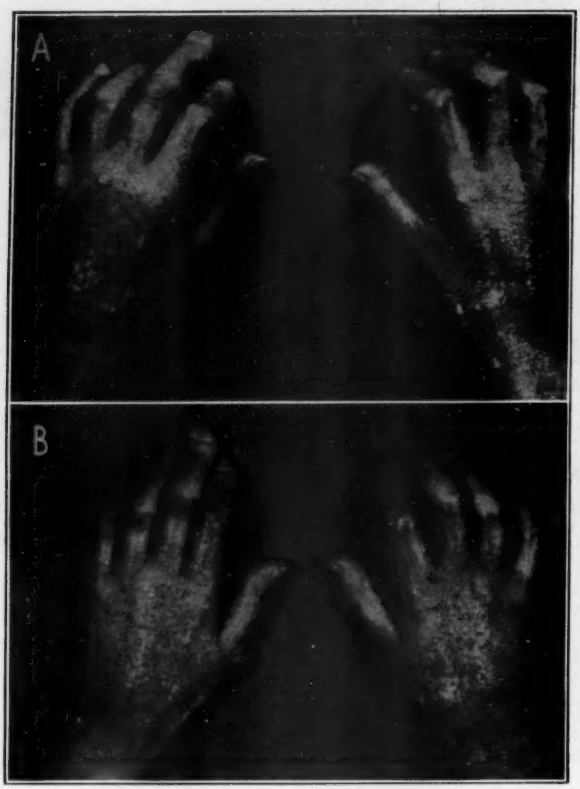

Fig. 8.—Photographs of the hands of patient 3. *A*, on April 13, 1948, at rest. *B*, on May 20; the hands are in the same position, but extension of the fingers has improved noticeably.

Physical examination gave the same results as before except that there was less edema and a greater range of motion in the hands. The skin of the forearms and legs was tightly bound to the underlying structures. Laboratory findings were similar to those previously noted.

Sodium paraaminobenzoate was administered in tablet form, 1.5 Gm. every three hours, and was well tolerated. On the fifth day, therapy was changed to the

administration of 2 Gm. every two hours of a half-and-half mixture of sodium paraaminobenzoate and potassium paraaminobenzoate. On this regimen the patient improved steadily. By May 28 edema could no longer be detected. The appearance of the skin, however, was more suggestive of scleroderma than before. There was some brownish pigmentation of the hands and lower legs, but the skin had become definitely looser. The patient felt rather well and was stronger. She was discharged to maintain treatment at her home in a distant state. It was learned in July that gradual improvement had continued although the disease process had not been completely reversed.

CASE 5.—A. J., a 24 year old white woman, was admitted to the Medical Service of the University Hospital on May 20, 1948, with the chief complaint of swollen joints. She had been well until December 1947, when an infection of the upper respiratory tract developed, with a cough productive of small amounts of mucoid sputum. The patient had remained in bed for two weeks; convalescence was slow, and there was persistence of malaise and easy fatigability. In early February 1948 the patient had become aware of puffiness of all her digits. The fingers were almost twice the normal size, and there was associated pain on motion and at rest. This swollen appearance persisted, and the fingers became somewhat stiff. After a few days, the patient noted red, asymptomatic "blotches" on her cheeks. About two weeks later the elbows, shoulders, knees, ankles and feet also became involved and were painful at rest and on motion. The ankles and toes were swollen. The patient also experienced chilly sensations and low grade fever, continued malaise and easy fatigability. Despite periods of rest in bed and various forms of therapy the involvement of the joints persisted and the patient was referred to the University Hospital.

Physical Examination.—This revealed that the skin of the hands and feet, across the bridge of the nose and over the malar prominences was hard, smooth and bound tightly to the underlying structures. There was limitation of motion of the fingers and wrists and of the ankles and toes, without localization to the joints. A fusiform swelling of the fingers was present but without evidence of active synovitis. Tenderness of the muscles was not elicited. The remainder of the examination gave negative results.

Laboratory Examination.—Extensive laboratory studies were performed. Pertinent findings included the following: The urinary excretion of creatine for twenty-four hours was 470 mg. on May 26. Roentgenographic studies of the hands and feet revealed juxta-articular osteoporosis of a moderate degree. A test for skin sensitivity to ultraviolet radiation gave a normal response. Biopsy specimens were taken on May 25 from the right gastrocnemius muscle and from the skin of the dorsum of the right foot. Microscopic examination of this material did not reveal diagnostic changes.

Course and Treatment.—Physical therapy was begun on May 20. This consisted of contrast baths to the hands and the application of radiant heat to the knees and ankles. Beginning on May 28 the patient received 3 Gm. every three hours of a mixture of equal parts of sodium paraaminobenzoate and potassium paraaminobenzoate. On this program there was definite subjective and objective improvement. The involved skin over the nose and cheeks became softer and more pliable. Pain became progressively less troublesome, and there was a better range of active and passive motion of the involved joints. The patient was discharged from the hospital on June 17, to continue therapy with paraaminobenzoic acid at home.

CASE 6.—A. E., a 23 year old white woman, was admitted to the University Hospital on June 28, 1948, complaining of swollen, painful joints. In August 1947 the patient had noted the outbreak of a burning, pustular rash on the face. This was accompanied by diffuse, but pronounced, facial swelling. Shortly thereafter acute pain developed in the shoulders and marked pain, tenderness and swelling appeared in the joints of the wrists, hands, fingers and ankles. Although the knees also became painful, there was no swelling. The course was characterized by progressive limitation of motion of the affected joints, especially of the hands and ankles. The patient's weight had gradually fallen from 135 to 118 pounds (61.2 to 53.5 Kg.), but there had been no chills, fever or anorexia. Amenorrhea had been present for three months prior to admission; previously, the menses had been regular.

Physical Examination.—This revealed the skin of the hands to be pale, shiny and atrophic. There was pronounced limitation of both flexion and extension of the fingers. The skin of the palms, the palmar fascia and the flexor tendons were also involved. Wrist motion was limited, partly as a result of involvement of the volar muscles of the forearm. A hard pitting edema was present over the feet and tibias. Subastragalar motion was virtually absent. There was no objective evidence of localized synovitis of any joint.

Laboratory Examination.—Routine laboratory examinations of the blood, urine and stool gave negative results. Roentgen examination of wrists, hands, knees and ankles revealed generalized osteoporosis, whereas the roentgenogram of the chest was negative. A twenty-four hour urine collection was found to contain 2,940 mg. of creatine. Biopsy specimens were taken from the right deltoid muscle and from the skin on the dorsum of the left hand. No pathologic diagnosis was suggested by this material. A test for skin sensitivity to ultraviolet showed a normal reaction after two thirds the normal exposure time.

Course and Treatment.—Despite the negative biopsy findings, the clinical findings were considered typical of scleroderma. The patient was treated with contrast baths to the hands and hot bakes to the ankles. On the seventh hospital day the administration of sodium paraaminobenzoate was begun. For the first two days 2 Gm. were given every three hours. This amount was well tolerated, and the dosage was increased to 3 Gm. on the same time schedule. The temperature, however, rose to 100 F. on the eighth day of therapy with paraaminobenzoic acid and increased progressively to 103 F. by the eleventh day. This was believed to be due to the development of drug sensitivity, and treatment with this compound was discontinued. The temperature promptly fell to normal. One week later a test dose of sodium paraaminobenzoate was administered to the patient, eliciting a prompt and severe febrile reaction. Evaluation was impossible in this case because of the development of drug fever after less than two weeks of therapy with paraaminobenzoic acid. There was noted a greater range of motion of the fingers, wrists and ankles, but this could not be attributed alone to the medication with paraaminobenzoic acid since physical therapy was also administered.

COMMENT

It is evident from the foregoing case reports that several patients had striking improvement during treatment with paraaminobenzoic acid. The question arises whether or not the improvement can be attributed to the administration of the paraaminobenzoic acid salts. In reference

to dermatomyositis, O'Leary and Waisman [4] stated that, as a rule, the tempo of onset predicates the rapidity of the course that will follow. Patient 1 was experiencing a rapid progression of the disease process at the time therapy with paraaminobenzoic acid was instituted. Improvement was noted within a few days. The possibility that this may have been due to spontaneous remission was considered. However, the patient gave the history of a relapse when she discontinued therapy with paraaminobenzoic acid at home, and the resumption of therapy was again accompanied with improvement, which was maintained. Furthermore, the biopsy specimens of muscle obtained during the radical mastectomy revealed the presence of active myositis after some ten months of treatment. This would suggest that there had been neither a cure nor a spontaneous remission but that the paraaminobenzoic acid compounds had in some manner suppressed the dermatomyositis.

The second patient had features of both dermatomyositis and scleroderma. He had been ill for three years with almost continuous fever, weakness and cutaneous changes when therapy with paraaminobenzoic acid was begun. Progressive improvement was observed during the five months of medication with paraaminobenzoic acid. The patient became afebrile, gained 34 pounds (15.4 Kg.) in weight and became increasingly stronger and more active. Moreover, the areas of sclerodermatous involvement had become thin, elastic and moist at the time of writing. There was also regression of the xanthomas and of the gynecomastia. In the light of present knowledge, it is difficult to attribute all these changes to the direct action of paraaminobenzoic acid; nevertheless, the temporal relationship between the administration of paraaminobenzoic acid and the improvement of this patient was highly suggestive.

The remaining 4 subjects had scleroderma. In regard to diffuse scleroderma, the course is characterized by periods of exacerbation and sometimes of remission, and death usually ensues after years of progressive debility.[5] In acrosclerosis, on the other hand, the prognosis is more favorable for life.[5b] Certain of the patients described herein may eventually be shown to belong to the latter category. At present, however, it is deemed necessary only to indicate that these patients presented a wide range of sclerodermatous involvement. Therapy with paraaminobenzoic acid was instituted from seven weeks to seven and a half years after onset; it is not possible, therefore, to compare the extent of improvement following treatment of these patients. It does

4. O'Leary, P. A., and Waisman, M.: Dermatomyositis: A Study of Forty Cases, Arch. Dermat. & Syph. **41**:1001, 1940.

5. (*a*) Baehr and Pollack.[1] (*b*) O'Leary, P. A., and Waisman, M.: Acrosclerosis, Proc. Staff Meet., Mayo Clin. **15**:702, 1940.

appear evident, however, that 3 of the 4 patients experienced definite benefit from therapy with paraaminobenzoic acid.

The most striking result was observed in H. J. (case 3), whose response is depicted in figure 6. This patient died of gastrointestinal hemorrhage, a complication which arose on an airplane flight during which nausea and retching were followed by hematemesis. Although nausea is occasionally encountered in patients receiving paraaminobenzoic acid, this patient had tolerated the compound well for five weeks. In retrospect, there was a long history of symptoms suggestive of peptic ulcer. Indeed, the patient had undergone abdominal surgery because of these complaints some ten years before. It is thought most probable that the patient bled from a peptic ulcer. In addition, it has been repeatedly observed [6] that diffuse sclerosis of the gastrointestinal tract may occur in this disease. It is possible, therefore, that the sclerodermatous process itself may have contributed to the terminal episode.

Patient 4 was treated during an acute, edematous and rapidly progressive stage of scleroderma. The process was apparently arrested; the edema subsided, and the skin became more pliable. The patient also regained considerable strength. Patient 5 had less extensive changes, and her response to paraaminobenzoic acid was similar, though not so striking. Drug sensitivity developed in the last patient, and administration of the compound was necessarily discontinued.

All the patients exhibited a 1 plus to 3 plus value for reducing substance in the urine while receiving therapy with paraaminobenzoic acid. The nature of this substance, which has been observed so far in all subjects receiving large amounts of paraaminobenzoic acid,[7] is being investigated; preliminary studies indicate that it is not glucose.

The mechanism of action of paraaminobenzoic acid in dermatomyositis and scleroderma remains obscure, as it is in lupus erythematosus.[2 a,c] It is possible that the effect of paraaminobenzoic acid in these diffuse diseases of collagen is supportive evidence of a close relationship between them. Such a conclusion should be reserved, however,

6. Lindsay, J. R.; Templeton, F. E., and Rothman, S.: Lesions of the Esophagus in Progressive Scleroderma, J. A. M. A. **123**:745 (Nov. 20) 1943. Goetz, R. H.: The Pathology of Progressive Systemic Sclerosis (Generalized Scleroderma), Clin. Proc. **4**:337, 1945. Olsen, A. M.; O'Leary, P. A., and Kirklin, B. R.: Esophageal Lesions Associated with Acrosclerosis and Scleroderma, Arch. Int. Med. **76**:189 (Oct.) 1945.

7. (*a*) Footnote 2. (*b*) Zarafonetis, C. J. D.; Andrews, G. A.; Meyers, M. C., and Bethell, F. H.: Para-Aminobenzoic Acid in Leukemia, Blood **3**:780, 1948. (*c*) Zarafonetis, C. J. D.; Curtis, A. C., and Kirkman, L. W.: Para-Aminobenzoic Acid in Lymphoblastoma Cutis and Mycosis Fungoides, to be published. (*d*) Zarafonetis, C. J. D.; Johnwick, E. B.; Kirkman, L. W., and Curtis, A. C.: Para-Aminobenzoic Acid in Dermatitis Herpetiformis, to be published.

since it has been demonstrated that paraaminobenzoic acid also affects, with varying degrees of success, such diverse conditions as chronic myelogenous leukemia,[7b] lymphoblastoma cutis[7c] and dermatitis herpetiformis.[7d] At this time, therefore, it does not appear warranted to speculate on possible mechanisms of action of paraaminobenzoic acid in these conditions. Much further study in these and additional cases will be necessary in order to determine and evaluate properly these effects of paraaminobenzoic acid.

SUMMARY

Two patients, 1 with dermatomyositis and the other with features of both dermatomyositis and scleroderma, improved greatly during prolonged therapy with paraaminobenzoic acid. Three of 4 patients with scleroderma experienced beneficial effects from similar treatment. It is concluded that additional investigation of paraaminobenzoic acid in dermatomyositis and scleroderma is warranted.

ANTIMICROBIAL THERAPY IN TYPHOID

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DURING the summer of 1948, an investigation of the antimicrobial therapy of typhoid was started in Guadalajara, México. The study was conducted as a joint project between investigators from the University of Guadalajara and the New York Hospital–Cornell University Medical College. Three drugs were studied: polymyxin B, aureomycin, and chloramphenicol.[1] Ample clinical and laboratory facilities were available at the Hospital Civil, the teaching hospital for the University of Guadalajara. Nevertheless, it was necessary to study approximately one half of the series of patients in their homes in the city or in the neighboring villages because of the reluctance of some patients to enter any hospital.

During the period of the study, a total of 51 patients with typhoid were treated with one of these drugs. Six of the series were treated in

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1. These drugs were supplied by their respective manufacturers: aureomycin, by Dr. Benjamin Carey, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.; chloramphenicol (chloromycetin®), by Dr. Elwood A. Sharp, Medical Director, Parke, Davis & Company, Detroit, and polymixin B (aerosporin®), by Dr. Gladys Hobby, Chas. Pfizer & Company, Inc., Brooklyn.

New York city [2] and 3 in México D. F., Mexico, by the same group of investigators. One additional patient was treated in San Juan, Puerto Rico, under the observation of a member of our staff.[3]

The city of Guadalajara is the capital of the state of Jalisco and, with a population of approximately 300,000, is the second largest city in Mexico.

The incidence of typhoid in Guadalajara is high. In the years 1943 to 1947 there was an average number of 152 cases reported annually and there is good reason to believe that an even larger number of cases escaped reporting.[4] The principal reason for the prevalence of typhoid in this locality is the fact that the central water supply system

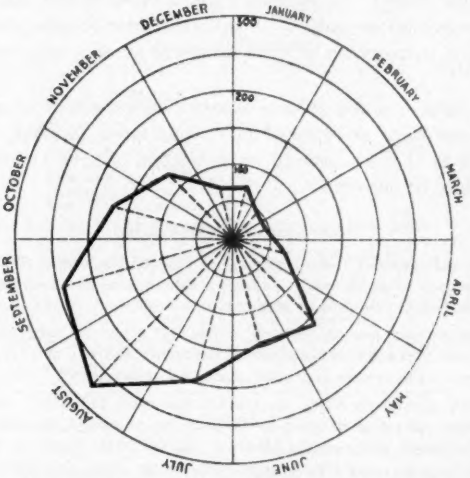

Chart 1.—Monthly incidence of typhoid in Guadalajara, 1935-1943 (from Ruiz Sánchez, F.: La fiebre tifoidea, Guadalajara, Jalisco, México, "Linotipográfica Guadalajara," 1944, p. 98, with permission). It will be noted that the incidence is highest during the months of July, August and September.

of the city, originally constructed for 100,000 persons, is now used by some 300,000. The system is antiquated, and the adjacent sewage system is said to be a frequent source of contamination to the water

2. One of these patients was treated at the Willard Parker Hospital for Infectious Disease and another at Bellevue Hospital (New York University Medical Service). The remainder were treated at New York Hospital.

3. Dr. Samuel Morones, of the University of Mexico, and Dr. J. Martinez, of the Regional Hospital, San Juan, Puerto Rico, granted permission to treat these patients.

4. Statistics supplied by the Health Department, State of Jalisco, México.

supply. As would be anticipated, the peak incidence of typhoid occurs during the rainy season (May to October, inclusive). The average monthly incidence of reported cases of typhoid for the years 1935-1943 may be seen in chart 1.

The character of the typhoid which is prevalent in Guadalajara is apparently no different from the typhoid observed in other localities. Because of its endemic character, the disease is particularly prevalent during childhood and early adult life. The development of infection after the age of 35 years is extremely rare and was not observed during the months of the present study.

The over-all case fatality rate varies considerably, depending on the age of the patient. In patients below 2 years of age, the disease is notably benign; before puberty it is of moderate severity, but during adolescence it is frequently of unusual severity and it may be severe in adults.

The incidence of the various familiar complications of typhoid is essentially the same as reported in various series of cases studied in other localities.[5] The over-all case fatality rate in Guadalajara is approximately 10 per cent.

MATERIALS AND METHODS

Selection of Patients.—At the beginning of the study, a method of chance selection was employed to decide which patients would receive which of the two drugs then available (polymyxin B, and aureomycin).

As serious toxicity was encountered in the first 2 patients who received polymyxin B, it was necessary to abandon this procedure and two successive series of patients received aureomycin and chloramphenicol respectively.

In the early part of the study, an attempt was made to exclude cases of more than twelve days' duration in order to diminish the possibility of natural recovery during the period of antimicrobial therapy. In the latter phase of the study, a deliberate attempt was made to include cases in the third and fourth weeks of disease provided that there were no signs of improvement at the time therapy was started.

The series of 51 patients[6] consisted of 23 females and 27 males. One was in the age group below 3 years; 20 were 3 to 12 years of age; 14 were 12 to 20, and 10 were 21 to 35. Six patients in the series were over 35 years of age, but 5 of this number were treated in New York. Their age range was 36 to 53 years.

All of the patients presented the characteristic picture of typhoid of all degrees of severity. The clinical diagnosis was confirmed by the demonstration of bacteremia in approximately 80 per cent of the patients and by the demonstration of a significant rise in antibody titer in the remainder.

5. Stuart, B. M., and Pullen, R. L.: Typhoid: Clinical Analysis of Three Hundred and Sixty Cases, Arch. Int. Med. **78**:629-661 (Dec.) 1946. Bercovitz, Z. T.: Clinical Tropical Medicine, New York, Paul B. Hoeber, Inc., 1944, p. 558.

6. Actually only 50 patients were treated but since G. W. was treated with two agents, he is considered as representing 2 cases.

Complete histories and physical examinations were obtained for all patients before the institution of antimicrobial therapy. In general, the patients were observed for twenty-four to forty-eight hours before treatment was started, but in some instances chemotherapy was begun before bacteriologic proof of diagnosis was obtained. During the acute phase of the illness, all Mexican patients were examined daily by at least two of the investigators (F. R.-S. and V. K.).

Several blood cultures were made for each patient before and during the first few days after the start of antimicrobial therapy, whether he was situated in the home or in the hospital. Despite considerable effort, it was not always possible to obtain blood cultures each day during the course of therapy.

Specimens of blood for antibody studies were drawn, and determinations of total leukocytes and erythrocyte counts were made at appropriate intervals before, during and after therapy.

TABLE 1.—*Untreated Summary Data on 46 Patients with Typhoid in New York Hospital (1932-1948)*

Age:	Range—9 months to 56 years Average age at onset—22.4 years
	Distribution 0-10 years—12 cases 11-20 years—14 cases 21-30 years— 5 cases 31-40 years— 7 cases 41-50 years— 4 cases 51-60 years— 4 cases
Diagnosis:	By blood culture: 40 of 46, or 86.9 per cent, positive By stool culture: Total done, 364 Total positive, 95 (26.1 per cent) Total cases with positive stool cultures, 32, or 69.8 per cent
Relapses:	10 of 46, or 21.7 per cent
Previous Vaccination:	Three cases (5 months, 5 years and 17 years and 3 weeks before onset of disease)
Complications:	11 of 46, or 23.9 per cent (including 1 intestinal hemorrhage, 2 cholecystitis and ? thrombophlebitis)
Deaths:	4, 8.7 per cent

Untreated Patients with Typhoid.—For purposes of comparison two groups of patients not receiving these agents were assembled. Fourteen were patients admitted consecutively to a hospital in Guadalajara in the period immediately preceding this study. Their disease corresponded in all respects to the description of typhoid in that region.

The other group consisted of 46 patients representing all patients with this diagnosis admitted to the New York Hospital in the preceding sixteen years. Certain data concerning these patients are presented in table 1. It is apparent that older persons tend to acquire the disease in New York, but aside from that, the disease otherwise conforms in severity and duration to the type of disease seen in Mexico. Five of this group received treatment with streptomycin but were, nevertheless, included.

Bacteriologic Technic.—Duplicate specimens of blood were cultured in brain-heart infusion and yeast extract broth. Approximately 6 cc. of blood was introduced into 60 cc. of medium. The cultures were incubated at 37 C. for a total period of seven days. The flasks were subcultured routinely on the second, third, fourth and seventh days, and identification procedures were carried out on any resulting growth according to the method used by the New York City Health Department.

Antibody titers (Widal test) were determined by two methods, by slide agglutination and by the tube dilution method in use at the New York Hospital. A comparative study of these methods, with use of several serums from each of 37 patients in this series, revealed that agglutination invariably occurred in higher dilution in tests done by the tube dilution technic. Results reported in this study, with few exceptions, were obtained by use of the tube dilution method.

Stool cultures were obtained whenever possible before treatment, and further examinations were made during and after treatement. Primary isolation was made on MacConkey's and bismuth sulfite agar.

Bioassays of Concentrations of Drug in Serum.—The chloramphenicol concentration was determined on the daily serum specimens of 8 patients taken during the period of therapy. The results showed good absorption of drug and corresponded to the serum concentrations obtained by other investigators after similar doses.

TABLE 2.—*Polymyxin B in Treatment of Typhoid*

					Polymyxin B			Results	
Patient	Age	Sex	Condition at Start of Therapy	Duration of Illness Prior to Treatment, Days	Mg./Day	Mg./Kg./ Day	No. of Days	Duration of Fever After Start of Treatment, Days	Comment
G. W.	35	M	Gravely ill; delirious	11	120	1.4	6	18	No evidence of toxicity; increasing severity of infection during treatment
E. M.	50	F	Gravely ill	11	225 200 300 500	4.3 3.2 5.8 9.5	1 1 1 20 hr.	16	Circumoral paresthesia, sustained hypotension last 2 days of treatment; no evidence of benefit from therapy
P. P.	25	F	Gravely ill; delirious	23	500	9.0	41 hr.	42 hr.	Death after acute collapse following fourth (250 mg.) dose
C. G.	36	M	Severe encephalitis; gravely ill	42	1,000	18.3	1	4	Excitement following first dose; complete anuria 5 days; gradual return of urine; definite clinical improvement following treatment

Serum concentrations of polymyxin B and of aureomycin were determined only on 1 patient each. Significant serum concentrations of the drugs were obtained in these cases.

Dosage Regimens.—The polymyxin B was administered intramuscularly, and the aureomycin and chloramphenicol were given by mouth. All doses were adjusted to the patient's weight on a milligram per kilogram basis. As several different regimens were used for each drug, details of each are presented under Results.

RESULTS

Polymyxin B.—Four adults (E. M., C. G., P. P., and G. W.) were treated with polymyxin B (table 2). All 4 patients were seriously ill, and 3 were in a continuous delirium. Bacteremia was present in 3 of the 4 at the time therapy was started and had been present previously in the other patient.

One of the 4 patients (G. W.) received daily doses of 1.4 mg. per kilogram of body weight (120 mg. daily) for a period of six days. Another (E. M.) received 3.2 to 9.5 mg. per kilogram of body weight during a four day period of therapy. This was 200 to 500 mg. per day. Chemotherapy was started on the eleventh day of illness [7] in both of these patients.

There was no evidence that the administration of the drug exerted any influence on the course of the typhoid in either patient. Fever and associated symptoms remained unchanged, as did the delirium present in 1 patient. Bacteremia persisted in patient G. W. for more than two days after the start of therapy and was present on the fourth treatment day in patient E. M. After the cessation of polymyxin B therapy, both patients slowly recovered from the typhoid and became permanently afebrile eighteen and sixteen days, respectively, after the start of therapy.

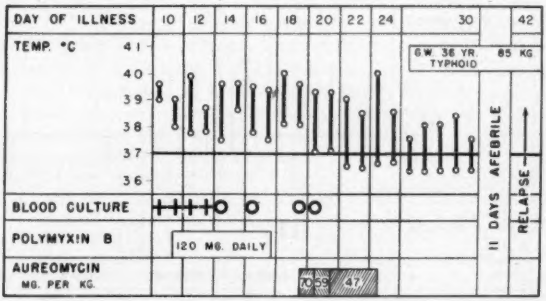

Chart 2.—Polymyxin B failed to influence the course in this severely ill American farmhand. Gradual improvement occurred after later treatment with aureomycin, but defervescence was slow. A severe relapse occurred with subsequent slow recovery. The patient was not retreated.

(One of these patients received aureomycin two days after cessation of polymyxin therapy. The course of events in this patient may be seen in chart 2.)

Manifestations of drug toxicity consisting of perioral paresthesias and sustained hypotension (systolic pressure 80 to 85 mm. of mercury) appeared in 1 patient (E. M.) during therapy but disappeared promptly when the use of polymyxin was discontinued. The particular lot of drug used in this patient contained appreciable quantities of histamine-like substances which were not present in the material administered to the other.

7. In the subsequent discussion the first day of known fever is arbitrarily designated as the first day of illness.

Because of the absence of discernible effect at the lower dose levels, other patients received total daily doses of 9.0 and 13.3 mg. per kilogram.

The third patient (chart 3) was a 35 year old man who had been desperately ill with bacteremic typhoid for forty-two days at the time polymyxin B was first administered. As may be seen in chart 3, his fever had shown no signs of remission during the week preceding trial of the drug and he was in a state of constant delirium with a fixed stare and gross jerky twitches of his extremities. During a twenty-four hour period he received 13.3 mg. per kilogram, or 1.0 Gm., of polymyxin B divided into three doses and administered by the intramuscular route. After the first injection he became acutely maniacal and required restraint, but the subsequent doses were well tolerated. Twelve hours after the first injection, however, a complete suppression of urine occurred. Moreover, the complete anuria persisted for a total period of five days. On the sixth day 10 cc. of clear urine was obtained by urethral catheterization and a slightly larger quantity on the seventh day. Thereafter, the patient voided naturally but passed about 2 liters of clear urine of fixed specific gravity each day.

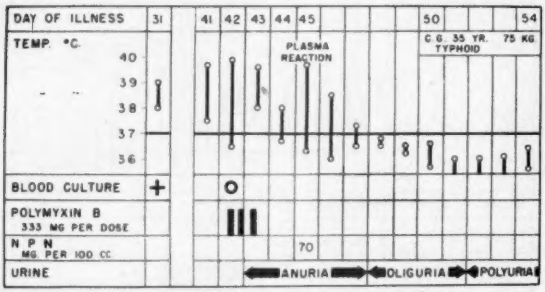

Chart 3.—This case illustrates the nephrotoxic properties of polymyxin B. At the start of treatment the patient was in a muttering delirium and very weak, with gross tremors and twitching of extremities. The initial injection was followed by a convulsive reaction. Anuria, oliguria and polyuria followed as indicated. The patient became rational and clinically was improved, despite the anuria and uremia. Polyuria with fixed specific gravity was observed for several weeks following this therapy. Recovery was otherwise complete.

Despite the complete suppression of urine after such a long-continued febrile illness, the patient presented a remarkably good appearance during the first part of the week following the initial administration of the drug. As may be seen in chart 3, his temperature rapidly fell to normal and remained there save for transient elevations associated with the administration of fluids by the intravenous route. Moreover, the delirium cleared appreciably, and during the latter part of the week the patient seemed to be rational and oriented. His blood pressure remained stable within normal limits, even when he had a moderate-sized hemorrhage from the bowel. No evidence of pericarditis appeared, but during the latter part of the week the patient's breath contained the odor of urine. On the third day of anuria the nonprotein nitrogen concentration of the blood was 70 mg. per hundred cubic centimeters.

Once the anuria was relieved, the patient recovered rapidly and apparently completely. Unfortunately, it was not possible to obtain adequate studies of his renal function prior to discharge from the hospital.

The fourth patient (P. P.) was a 25 year old woman who had been ill for twenty-three days when polymyxin B therapy was started. She was acutely ill and was in a constant delirium with a temperature of 39 C. (102.2 F.), a profuse watery diarrhea and Salmonella typhosa bacteremia. On the evening of admission to the hospital she was given 200 mg. of polymxyin B by intramuscular injection (approximately 3.6 mg. per kilogram). Careful observation during the ensuing four hours revealed no evidence of toxicity. The following day she appeared slightly better and was given a total of 500 mg. of polymyxin B in two equally divided doses in the morning and the evening. The following morning, although still acutely febrile, she did not appear to be critically ill in any respect. Accordingly, at 9 a.m. she received another 250 mg. injection of polymyxin B by the intramuscular route. Forty-five minutes later she complained of a sudden sensation of weakness. On examination, she was conscious and appeared apprehensive. Her radial pulse was 80 beats per minute, and frequent premature ventricular contractions were present. Her respirations were slow and deep (approximately 12 to 15 per minute). The skin was warm and of good color, and no unusual sweating was present. There were no convulsive seizures or other evidences of hyperexcitability. Her condition remained essentially unchanged for one-half hour, when she suddenly died.

Postmortem examination, performed within one hour of death, revealed widespread changes characteristic of typhoid. There was no evidence, however, of any intestinal hemorrhage or perforation. Examination of the heart revealed 150 cc. of serous pericardial fluid, and in the myocardium were observed small focal infiltrations with mononuclear cells and degeneration.

Two blood cultures obtained during the forty-two hours from the first injection of polymyxin to death were positive for S. typhosa, as were cultures of the stool.

It is believed that the paresthesias and hypotension in patient E. M., the protracted anuria in patient C. G. and the death of the patient just described were all a consequence of polymyxin B toxicity.

Summary: The clinical and bacteriologic course of typhoid was not discernibly affected by the intramuscular administration of polymyxin B to 3 of 4 patients seriously ill with the disease. The fourth patient recovered during the course of the serious drug reaction, but it was not possible to relate the recovery to antimicrobial activity of the drug.

Aureomycin.—Thirty-four patients with typhoid received aureomycin by the oral route for periods of six to ten days (table 3).

Two patients died, both of intestinal complications. The remaining 32 patients all recovered, and, except for a moderately severe intestinal hemorrhage in 1, none of the familiar complications of typhoid appeared.

The course of the infection during aureomycin therapy followed one of four patterns: rapid recovery; gradual recovery; unchanged with eventful recovery, and death. Accordingly, these categories will be used in the subsequent discussion.

Deaths: The two deaths were those of a 21 year old man and a 14 year old child.

The adult patient (chart 4) was a student in a theological seminary who was severely ill on the twenty-first day of bacteremic typhoid, when aureomycin therapy was started. He received 6 Gm. during the first twenty-four hours and 4 Gm. (or approximately 60 mg. per kilogram) daily thereafter for a total period of six days. There was no change in his condition during the first two days of therapy other than the appearance of profuse epistaxes. On the third day, as may be seen in chart 4, there was a sharp fall in temperature, but it was almost immediately followed by the appearance of an intestinal hemorrhage of approximately 1 liter. Despite the continued administration of aureomycin, his condition steadily grew worse, and evidence of intestinal perforation appeared on the sixth day of therapy. Accordingly, an operation was performed, at which a 25 cm. portion of the ileum was removed.

Examination revealed at least two large necrotic areas through which it was possible to demonstrate a perforation and several smaller ones over which the serosa was the only remaining intact tissue membrane.

Antimicrobial therapy was changed to use of penicillin and streptomycin because a generalized peritonitis was present and the effectiveness of aureomycin in this type of infection had not yet been established. The patient's condition steadily became worse, however, and he died forty-eight hours following the laparotomy.

The failure of aureomycin in the dosage used to influence the course of this infection was particularly clearcut, for the perforation did not occur until after six days of treatment. Moreover, as may be seen in chart 4, bacteremia persisted for at least seventy-two hours after the start of aureomycin therapy.

In the other fatal case, the failure of antimicrobial therapy was less clearcut. The patient was an extremely debilitated 14 year old child who had been ill intermittently for five weeks with what was apparently a succession of illnesses following acute pharyngitis. She had been discovered to have thrombopenic purpura two years previously, and the early phase of this illness was associated with frequent purpuric episodes with uterine bleeding. It was not possible to establish the onset of the typhoid with precision, but the patient was acutely febrile with S. typhosa bacteremia at the time aureomycin therapy was instituted.

During a thirteen day period, in which the patient received 222 mg. of aureomycin per kilogram of body weight each day, some improvement was noted. Bacteremia disappeared, and defervescence gradually occurred. Nevertheless, a moderate degree of abdominal distention appeared and persisted. In the second week of aureomycin treatment, the abdominal distention increased markedly, although the patient by this time was afebrile. As no evidence of intestinal perforation was present, it was considered inadvisable to perform a laparotomy. The patient's condition steadily became worse, and she died on the third day after the cessation of aureomycin therapy. It was not possible to obtain permission for a postmortem examination. It is reasonable to assume, however, that the abdominal distention was related to intestinal involvement by the typhoid.

Rapid Recovery During Aureomycin Therapy: Rapid recovery with disappearance of fever and symptoms within seventy-two hours was observed in only 4 of the patients who received aureomycin. The most rapid recovery in the entire aureomycin series occurred in a 3 year old girl with bacteremic typhoid who was started on aureomycin

TABLE 3.—*Aureomycin in Treatment of Typhoid*

Patient	Age	Sex	Condition at Start of Therapy	Duration of Illness Prior to Treatment, Days	Aureomycin			Results		
					Gm./Day	Mg./Kg./ Day	No. of Days	Duration of Fever After Start of Treatment, Days	Clinical Evaluation *	Comment
T. Ro.	7	F	Acutely ill	4	3	200	1	16	3	Unimproved after treatment
					2	133	3			
					3	200	2			
L. Cr.	5	M	Gravely ill	6	3	200	1	7	1	Significant recovery during treatment; relapse 11 days after finishing treatment
					2	133	5			
R. Ur.	3	M	Acutely ill	7	4	333	1	4	2	Improved after treatment; relapse eleventh afebrile day
					3.25	266	5			
R. Vi.	7	M	Acutely ill	7	6	285	3	9	3	No evidence of drug effect
					4	190	3			
					6	285	6			
G. Lu.	9	M	Acutely ill	8	6	180	2	10	3	No evidence of drug effect
					4	120	4			
H. To.	12	F	Gravely ill	8	4	133	1	13	3	Improved after treatment but fever persisted
					3	100	5			
A. Ur.	8	F	Acutely ill	8	4.2	200	1	6	3	No evidence of drug effect; relapse at 11 days
					3.8	180	5			
E. B.	3	F	Acutely ill	9	6	500	2	2	1	Rapid recovery early in disease, suggesting drug effect
					1	83	4			
F. Me.	32	F	Acutely ill	9	24	353	5	3	1	Prompt improvement, probably drug effect
					12	176	1			
N. Ca.	2½	M	Acutely ill	9	3.5	266	8.6	14	3	No evidence of drug effect
L. Gom.	12	M	Acutely ill	10	6	180	1.5	13	3	Moderate improvement while treated; relapse on ninth afebrile day
					4	120	4.5			
E. Pa.	7	M	Acutely ill	10	4	160	1	4	1	Rapid recovery early in disease, possibly drug effect
					3	120	5			
J. C. (N. Y.)	46	M	Acutely ill	10	6	92	1	7	2	Reduction in fever during treatment; relapse in 7 days
					12	184	3.5			
					6	92	1			
					3	42	1.2			
					1	15	1			
P. Al.	25	M	Acutely ill	12	6	150	5	8	2	Moderate rapid improvement, possibly drug effect
					4	66				
E. G.	13	M	Gravely ill	12	4	120	1	31	3	Stormy course; no evidence of drug effect; relapse in 7 days
					3	90	5			
G. Ma.	14	M	Gravely ill	12	5	100	2	12	2	Gradual improvement; impression that drug helped
					4	80	4			
A. Del.	6	F	Acutely ill	14	4	190	1	8	3	No evidence of drug effect
					3.2	150	5			
H. Va.	14	F	Acutely ill	15	6	120	1	10	2	Improved under treatment
					4	80	5			
J. Ro.	10	M	Acutely ill	16	3	165	1	11	3	Continued fever under treatment; no evidence of drug effect
					2	110	3			
					3	165	2			
C. Gu.	35	F	Gravely ill	17	6	120	1	11	3	Serious bowel hemorrhage prior to treatment; fever continued throughout treatment
					4	80	5			
A. G. (N. Y.)	43	F	Gravely ill	17	1.050 (i. v.)	18	3	11	3	Remained acutely ill and febrile throughout treatment
					12	200	4			
G. Bo.	9	F	Acutely ill	17	6	260	2.5	11	3	No evidence of drug effect
					8	348	3.5			
J. Bo.	6	M	Gravely ill	18	6	400	6	6	2	Necrotic ulcer (noma) of mouth present on admission; moderate rapid improvement with healing of ulcer, probably drug effect

TABLE 3.—*Aureomycin in Treatment of Typhoid—Continued*

Patient	Age	Sex	Condition at Start of Therapy	Duration of Illness Prior to Treatment, Days	Aureomycin			Results		
					Gm./Day	Mg./Kg./ Day	No. of Days	Duration of Fever After Start of Treatment, Days	Clinical Evaluation *	Comment
E. Mo.	10	F	Acutely ill	19	6 4	240 160	1 5	2	3	No drug effect evident
G. W.	35	M	Gravely ill	19	6 5 4	70 59 47	1 1 4	13	3	Less fever during treatment; relapse at 11 days
L. B.	21	M	Gravely ill	21	6 4	85 57	1 5		4	Hemorrhage, perforation operation and death following treatment
Ca. B.	15	F	Gravely ill	21	6 4	120 80	1 5	8	2	Moderate severe bowel hemorrhage during treatment; good recovery, possibly drug effect
J. U.	21	M	Acutely ill	22	6 4	92 61	1 5	9	3	Gradual recovery; no evidence of drug effect
N. Mas.	14	M	Gravely ill	23	6 4	285 190	3 7	18	3	Reduction in temperature during treatment; many symptoms persisted
C. Re.	19	M	Gravely ill	24	5 4	80 64	2 4	6	2	Improvement noted on first day of treatment; good recovery
H. R.	35	M	Gravely ill	28	9 18 6	143 285 96	3.8 6.0 2.0	10	2	Very large bowel hemorrhage prior to treatment; fairly rapid recovery, possibly drug effect
J. B.	7	M	Gravely ill	29	6	333	6	5	2	Rapid recovery, possibly drug effect
E. Ca.	7	M	Gravely ill	40	4 3	200 150	1 5	45	3	No evidence of drug effect, continued fever; probable perforation prior to treatment with abdominal abscess
Ja. U.	14	F	Gravely ill	38	6 4 6	222 106 222	1 7 5	13	4	Died on fifteenth day after start of treatment with severe abdominal distress complicated by thrombopenic purpura

* Grade 1 indicates rapid recovery; 2, gradual recovery; 3, unchanged during treatment, and 4, death.

therapy on the ninth day of illness. As may be seen in chart 5, seventy-two hours after the start of therapy the patient was afebrile and asymptomatic, and bacilli could no longer be cultured from her blood. The recovery was maintained after the completion of therapy.

It should be noted that this patient was in an age group in which typhoid is generally not unduly severe and that she received 500 mg. of aureomycin per kilogram during the first forty-eight hours of treatment. This was the largest dose of aureomycin, on a weight basis, which was used in the entire study and would represent 25 to 35 Gm. daily in an adult of average size. Chart 6 illustrates the course of a young boy who made a rapid recovery, and who received doses of aureomycin that did not exceed 120 mg. per kilogram per day. Although this patient was acutely ill with many rose spots and palpable spleen, the stool and blood cultures did not show the organism. Weil-Felix aggluti-

nation reactions were negative, and the Widal titer was sufficiently elevated in this nonvaccinated patient to establish the diagnosis.

Gradual Recovery During Aureomycin Therapy: The next most frequently observed pattern during aureomycin therapy was a gradual

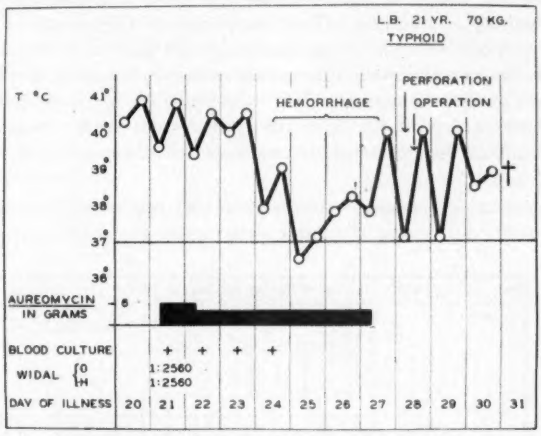

Chart 4.—Intestinal hemorrhage began during the fourth day of aureomycin therapy in a critically ill bacteremic patient with typhoid. Despite the drug, perforation, operation and death as a result of generalized peritonitis followed in succeeding days. This is in marked contrast to the favorable course of C. R., who received chloramphenicol.

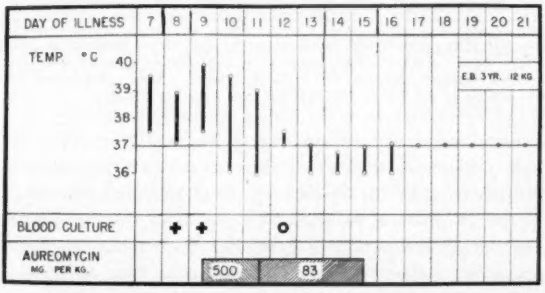

Chart 5.—This 3 year old girl received the highest doses (in milligrams per kilogram of body weight) of aureomycin given in this series. The patient was greatly improved and almost afebrile by the third day of treatment. Complete recovery ensued and was maintained. This is considered to be the most favorable result among the aureomycin-treated patients.

recovery during the week following the start of therapy. A course of this type was observed in approximately 32 per cent of the patients in the series (10 of 34).

There was no perceptible change in the condition of any of these patients during the first forty-eight hours of aureomycin therapy. By the third or, more frequently, the fourth day of treatment a definite improvement would be apparent. The characteristic apathetic typhoid facies would disappear and be replaced by a more alert and sometimes by a smiling countenance. The temperature would remain at normal or subnormal levels for an appreciably greater portion of the day, and, despite the gastric irritation frequently caused by the drug, there would be some return of appetite. With the onset of this improvement on the third or fourth day after the start of aureomycin treatment, it would appear that the issue was no longer in doubt and that recovery would shortly occur.

Nevertheless, complete defervescence did not usually occur at this time, and even during the latter part of the first week of treatment

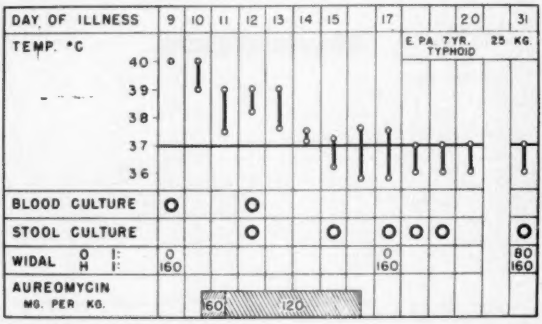

Chart 6.—This 7 year old boy presented high fever, abdominal distention and many rose spots. Despite this, neither of two blood cultures was positive and several stool culture yielded no typhoid bacilli. After institution of therapy, recovery gradually occurred without complications or relapse.

the patient's temperature would rise to 39 or 40 C. (102.2 or 104 F.) for brief periods each day. Defervescence which was maintained, however, occurred on the average by the eighth day after start of treatment in all 10 of these patients who presented the pattern of gradual recovery during the period of administration of aureomycin. As the disappearance of other symptoms preceded the final defervescence, the course from this point on was uneventful.

It will be noted by reference to table 3 that the patients who showed a pattern of gradual recovery were ill for perods of four to twenty-nine days before treatment was started, and there appears to be no relationship between recovery and duration of illness before treatment in this group. In chart 7 may be seen the course of a patient exemplify-

ing this type of recovery. A significant feature of this man's treatment was the persistence of bacteremia for six days after start of aureomycin therapy.

Course of Infection Unchanged During Aureomycin Therapy: In approximately 53 per cent of the patients, 18 of 34, there was no discernible improvement during six to ten days of aureomycin therapy. Except for the 2 fatalities, mentioned previously, all these patients eventually recovered during the week or ten days following the cessation of the aureomycin. In many of these patients, bacteremia was not present at the start of therapy. Nevertheless, many of them were seriously ill and remained so throughout the period of the administration of aureomycin.

Representative examples of this pattern of unchanged course during aureomycin therapy may be seen in charts 8 and 9.

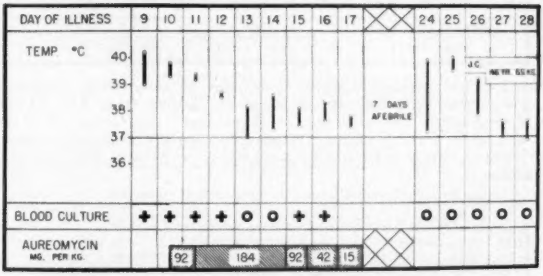

Chart 7.—Gradual clinical improvement and defervescence occurred in this severely ill man after the start of aureomycin therapy. Despite improvement and a virtually normal temperature, the blood culture revealed S. typhosa on the sixth day of aureomycin treatment. Nausea and vomiting prevented further therapy, and relapse occurred after one week without fever.

Relation Between Pattern of Course During Aureomycin Therapy and Duration of Illness: Since it had required more than one week in almost all these patients for complete defervescence to occur, it was evident that statistical evidence of therapeutic activity could be obtained more easily from patients who were sick for a relatively short time before therapy was begun. Exclusive of the 2 fatalities, it was possible to divide the entire aureomycin series into two groups, consisting of 16 patients in whom therapy was started between the fourth and twelfth days of illness and another 16 patients in whom therapy was started between the fourteenth and forty-ninth day of illness (chart 10).

As may be seen in chart 10, there was only a slight difference (one day) between the two groups in the average duration of fever after the administration of aureomycin was started. There was a con-

siderable difference between the two groups, however, in the total duration of febrile illness. In the group treated on or before the twelfth day, the average for total duration of febrile illness was slightly less than twenty days, whereas in the group treated later in the course of the illness the average for the total duration of febrile illness was approxi-

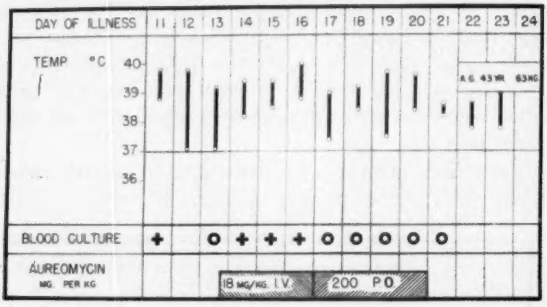

Chart 8.—This patient received high doses of aureomycin intravenously and orally, with serum concentrations of the drug ranging from 5 to 10 micrograms per cubic centimeter. Nevertheless, no improvement was observed in the clinical course, and high fever persisted. Natural recovery gradually occurred. There was no relapse, but repeated stool cultures were positive for S. typhosa after defervescence.

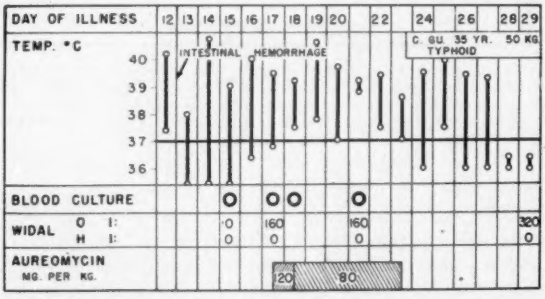

Chart 9.—This patient's course was complicated by severe intestinal hemorrhage and shock. When treatment was started a few days later, she was critically ill with high fever. No alteration in the course of her infection was observed after administration of aureomycin. Several days after treatment she became afebrile, and gradual recovery ensued.

mately thirty-three days. The latter value is comparable to the values 32.8 and 38.3 days in two series of patients with untreated typhoid in the same chart. It is distinctly unlikely that in such a small total series all the infections of short natural course would have fallen by chance

into the group in which treatment was started between the fourth and the twelfth day.

When these data were statistically analyzed, it was found that the twenty day mean duration of illness was significantly [8] (according to *t* probability tables) shorter than that of the untreated patients. It was further found that the period after treatment of this group of patients was significantly less than the mean febrile period after hospital admission among the untreated patients.

Relapses: In 7 of the 34 patients who received aureomycin, a relapse of the infection occurred after a period of complete remission of all evidences of infection. The incidence of relapse in the aureomycin-treated patients (7 of 34) is comparable to the incidence (10 of 46) observed in the untreated patients in the New York Hospital group.

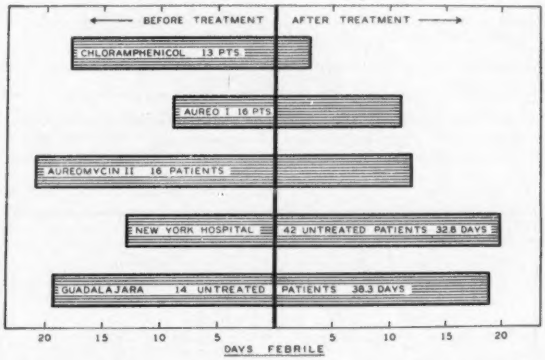

Chart 10.—The total duration of febrile illness in aureomycin-treated patients of group I, for whom treatment was started before the twelfth day of illness, was significantly shorter than in the two groups of untreated patients. The period of febrile illness after start of therapy in patients receiving chloramphenicol was significantly less than in the aureomycin-treated patients—groups I and II (for whom treatment was started after the twelfth day of illness)—and in the patients receiving no therapy.

Moreover, the interval between defervescence and the onset of relapse was very similar, being ten and thirteen days, respectively, for the aureomycin-treated and the untreated series.

An example of a relapse following use of aureomycin may be seen in chart 7. Bacteremia was present during relapse in 3 of the 4 patients from whom blood cultures were obtained. Four of the patients received additional aureomycin therapy during the second febrile episode. The

8. Mills, F. C.: Statistical Methods. New York. Henry Holt & Company, 1938, pp. 604-605.

relapses were mild and in most cases consisted of several days of fever. Patient G. W. was severely ill during relapse, however, and his course was complicated by arthritis which persisted for several weeks.

Relation of Large Doses of Aureomycin to Rapidity of Recovery: Three dosage regimens were used successively: 47 to 100 mg. per kilogram; 101 to 200 mg. per kilogram, and 201 to 500 mg. per kilogram. Approximately one third of the 34 patients were treated on

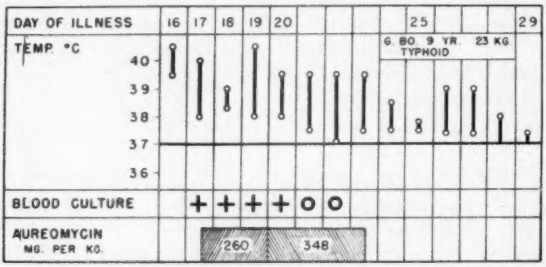

Chart 11.—This acutely ill child with repeatedly positive blood cultures failed to improve appreciably after high doses of aureomycin. Defervescence occurred gradually several days after cessation of treatment, with complete recovery.

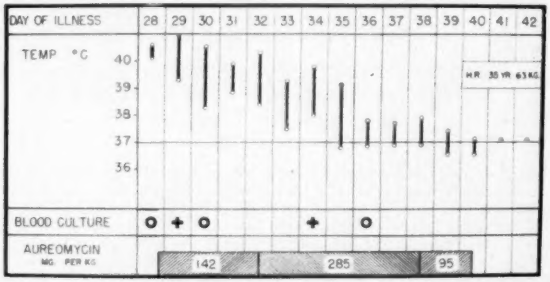

Chart 12.—This critically ill adult received 9 Gm. of aureomycin daily for almost four days, followed by 18 Gm. daily for six additional days. Despite this therapy, the blood culture was positive on the sixth day of treatment, and defervescence required ten days from the start of aureomycin treatment.

each regimen. A definite impression was gained that the lowest dose regimen was less often associated with recovery during therapy. Even with the higher doses, however, the rate of recovery was not uniform, as may be seen in the chart of a representative patient, G. Bo. (chart 11).

In chart 12 may be seen the course of the infection in an adult who received 18 Gm. of aureomycin daily for a period of six days.

The patient was a 35 year old man who had been febrile for four weeks but who was seriously ill with delirium, bacteremia and fresh crops of rose spots at the time aureomycin therapy was started. No improvement occurred during a four day period in which 142 mg of drug per kilogram of weight was administered daily. Accordingly, the dose was increased to 285 mg. per kilogram, or 18 Gm., each day. Seventy-two hours after the increase in dosage, defervescence occurred and was maintained thereafter.

It should be noted, however, that bacteremia persisted for forty-eight hours after the marked increase in dosage and that the onset of recovery appeared late in the disease and after a total period of aureomycin therapy of one week's duration.

Course of Bacteremia During Aureomycin Therapy: The course of bacteremia in 25 patients during the administration of aureomycin may be seen in table 4. In several patients, S. typhosa was isolated from the blood before therapy but blood cultures were not obtained (or they were sterile) on the day therapy was started. Moreover, it was

TABLE 4.—*Course of Bacteremia in 25 Patients with Typhoid Treated with Aureomycin*

Hours After Start of Treatment	Blood Cultures	
	Total Number	Number Positive
At start of therapy	21	15*
24	18	12
48	12	8
72	12	6
96	8	3
120	6	0
144	3	1

* The 10 patients whose cultures were not positive at the start of treatment were bacteremic before or after its beginning.

not always possible to obtain blood cultures on each day following the start of therapy. Furthermore, it is well recognized that the bacteremia of an untreated patient with typhoid may not persist throughout the entire period of acute illness. Thus, although the results presented do not reflect the true incidence of bacteremia during therapy, they serve to reveal that bacteremia persisted for two to four days in an appreciable number of patients. As may be seen in table 4, after the start of aureomycin therapy, bacteremia was demonstrable for twenty-four hours in 12 patients, for forty-eight hours in 8 patients, for seventy-two hours in 6 patients and for four and six days in 3 and 1 patients, respectively.

The results of the studies of antibody titers and stool cultures are presented in a subsequent part of this paper.

Emergence of Drug-Resistant S. Typhosa Organisms: S. typhosa organisms isolated from the blood of 3 of the patients who had relapses after aureomycin treatment (R. Ur., E. Gz. and L. Gom.) were found to be inhibited by the same concentration of aureomycin

necessary for inhibition of the strains isolated from these patients in their initial illness (1.6 micrograms per cubic centimeter).

Summary: Two of 34 patients with typhoid who received aureomycin died as a consequence of their disease, and the remainder recovered without acquiring any of the familiar complications of the disease. It was possible to show in the patients who received aureomycin before the twelfth day of their disease that the total mean duration of febrile illness was significantly shorter than in two groups of untreated patients and that the duration of illness after start of treatment in these patients was significantly less than the febrile period after admission to the hospital among the untreated patients. As the rate of the recoveries was not uniform and they were seldom dramatic, it is not certain, although probable, that the differences described are attributable to the administration of the drug.

Chloramphenicol.—Thirteen patients with typhoid were treated with chloramphenicol. The diagnosis was established by demonstration of bacteremia in 12 and by antibody determinations and positive stool culture in the other. As may be seen in table 5, 8 of the patients were in the age group 7 to 14 years and the remainder were 16 to 53 years of age. The duration of illness at the time antimicrobial therapy was started was six days in 2 cases, seven days in 1 case and twelve to thirty-nine in the remaining 10 cases. As in the previous series, all the patients were acutely ill with the characteristic manifestations of typhoid when therapy was started.

Chloramphenicol was administered by mouth in five or six divided doses each day. In general, the regimen used consisted of 100 mg. per kilogram daily for the first two or three days and 50 mg. per kilogram thereafter for a total period of seven to ten days. At times, however, modification of this regimen was made, usually because the supply of the drug was necessarily small.

Regardless of the previous duration of illness or the presence or absence of bacteremia, the average period of fever and symptoms after the start of chloramphenicol was 3.2 days and there were no deaths or complications of the disease (chart 10).

Pattern of Recovery: The pattern of recovery was remarkably uniform. During the first forty-eight hours after the start of chloramphenicol therapy there was no discernible change in the condition of 12 of the 13 patients. The temperature remained high, and delirium and painful abdominal distention, present in many of the patients, continued. Within the next twenty-four hours (i. e., during the third day of treatment), however, an abrupt recovery occurred. The speed and extent of this recovery which appeared during the third day was comparable in every way with the familiar crisis of pneumococcus pneumonia.

In charts 13 and 14 may be seen representative examples of the course of the typhoid during the administration of chloramphenicol.

Patient N. G. (chart 13) was a 14 year old school boy who was critically ill on the eighteenth day of bacteremic typhoid when chloramphenicol therapy was

TABLE 5.—*Chloramphenicol in Treatment of Typhoid*

								Results	
				Duration of Illness Prior to Treatment, Days	Chloramphenicol			Duration of Fever After Start of Treatment, Days	
Patient	Age	Sex	Condition at Start of Therapy		Gm./Day	Mg./Kg./Day	No. of Days		Comment
J. Go.	12	M	Gravely ill	6	2.6 1.3 0.6	100 50 25	4.0 3.0 3.0	3	Rapid recovery after treatment
G. C.	8	M	Gravely ill	6	3.0 2.0	125 83	1.0 5.0	1	Overnight defervescence after start of treatment; relapse on fifteenth afebrile day
Y. Lu.	7	F	Gravely ill	7	2.75 1.0	137 50	1.0 1.5	2	Remarkable remission in 48 hours after start of treatment by crisis; despite only 2.5 days of treatment; no relapse
H. Ro. (N. Y.)	36	F	Gravely ill	12	7.5 3.0 2.0	90 33 22	1.0 4.0 2.5	3.25	Recovery by crisis on third treatment day; relapse on seventeenth afebrile day; retreated with good result
L. Ru.	8	F	Acutely ill	13	2.75 1.5	137 75	1.0 6.0	5	Steady recovery; no relapse
A. Si. (N. Y.)	53	F	Acutely ill	15	6.0 1.5	100 25	2.5 6.0	3.25	Rapid recovery; greatest improvement during third treatment day
D. C. (P. R.)	11	F	Gravely ill	15	4.0 3.0 0.75		1.0 2.0 0.5	2.5	Rapid recovery during third day of treatment; short treatment period followed by relapse in 8 days; retreated with high doses of chloramphenicol; good result
N. G.	14	M	Gravely ill	18	3.00	100	6.0	3.5	Remarkable recovery in an extremely ill patient; relapse on nineteenth afebrile day
Y. Mi. (N. Y.)	41	F	Acutely ill	21	2.25	50	6.5	6	Given low dose; low grade fever persisted for 5 days; recovery virtually complete by third day
A. Lo.	16	M	Acutely ill	27	5.0	100	2.5	1.5	Prompt recovery sustained with only 2.5 days of treatment
M. Ro.	7	F	Acutely ill	29	1.8 0.75	100 40	3.0 5.0	3	Defervescence by lysis; rapid clinical improvement
G. He.	14	F	Gravely ill	30	4.75 1.25	100 25	3.5 3.5	2	Very sick patient with defervescence by crisis about forty-eighth hour of treatment; clinical recovery in proportion
C. R.	19	M	Gravely ill	39	5.0 2.7	100 60	2.0 0.5	2	Remarkable recovery after perforation of intestine with gross soiling of peritoneum; temperature not in excess of 38.6 C. after operation

started. During the first forty-eight hours of antimicrobial therapy, he showed no evidences of improvement. The temperature remained high, delirium continued and severe and apparently painful abdominal distention persisted. Shortly after the forty-eighth hour, however, the onset of defervescence began, and defervescence was completed by the end of the ensuing day. Simultaneous with defervescence there was a rapid disappearance of the delirium and the abdominal distention, and the patient became alert, cheerful, completely rational and hungry.

Patient H. Ro. (chart 14) was a 36 year old woman who first received chloramphenicol on the twelfth day of bacteremic typhoid. Forty-eight hours after the start of therapy she was still acutely febrile and delirious and had moderately severe abdominal distention. Twenty-four hours later (i. e., at the end of the third day of treatment), she was afebrile, was completely rational and had a soft and nontender abdomen.

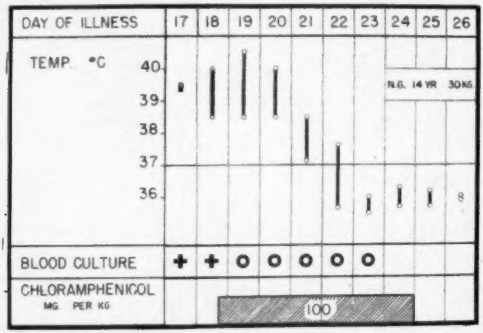

Chart 13.—This patient's course characterizes the forty-eight hour lag period before improvement after the start of chloramphenicol therapy. He was severely ill and remained so until the third day of treatment, when recovery was almost by crisis. Relapse later occurred.

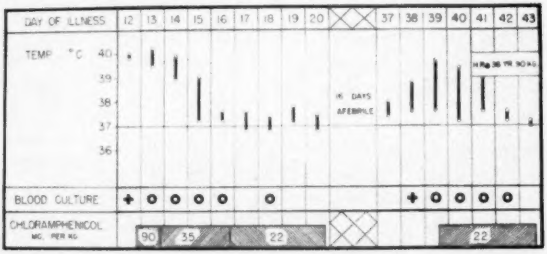

Chart 14.—This patient responded after a forty-eight hour lag period after the start of chloramphenicol therapy. Relapse occurred after sixteen days without fever and despite eight days of therapy with chloramphenicol. Retreatment was once again followed by a forty-eight hour lag period before improvement was observed.

Forty-eight Hour Lag Before Onset of Recovery: Only 1 of the 13 patients failed to show this forty-eight hour lag in the onset of improvement after the start of the antimicrobial therapy. This patient (G. C., chart 15) was an 8 year old boy with bacteremic typhoid for whom administration of chloramphenicol was started on the sixth day of illness, at a time when his temperature was 41 C. (105.8 F.). Defer-

vescence occurred overnight and was accompanied with complete disappearance of symptoms.

It should be noted that this unusually rapid recovery occurred in an infection of only short duration at the time antimicrobial therapy was started.

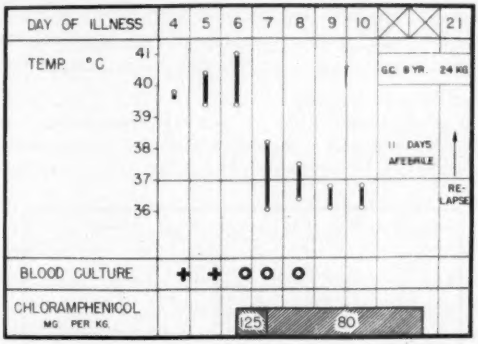

Chart 15.—This patient, treated on the sixth day of the disease, improved overnight. This was the only such prompt response observed in the chloramphenicol-treated patients. The relapse indicated was mild, and no drug was administered.

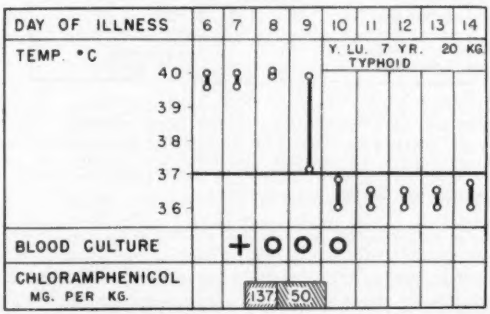

Chart 16.—This acutely ill Mexican girl recovered by crisis in her third day of treatment with chloramphenicol. Recovery was sustained, despite the administration of the drug for only sixty hours.

In 1 instance, the antimicrobial therapy was administered only until the period when the onset of recovery would be anticipated, i. e., for two and one-half days. The patient (chart 16) was a 7 year old girl who was acutely but not critically ill on the seventh day of illness, when chloramphenicol treatment was started. Fresh rose spots and bacteremia were present immediately before treatment. A total of 4.25 Gm. of chloramphenicol was administered during a total period of

sixty hours. As in the other patients, there was no evidence of improvement during the first forty-eight hours of antimicrobial therapy. During the third day, however, despite the cessation of chloramphenicol, the characteristic abrupt and complete recovery occurred. It is noteworthy that there was no return of fever or other evidence of infection during the succeeding days in which no antimicrobial therapy was administered.

Complications: In none of the patients did any of the complications of typhoid develop after therapy with chloramphenicol. In 1 instance, however, the serious complications of intestinal hemorrhage and perforation were present at the time antimicrobial therapy was started.

The patient (C. R., chart 17) was a 19 year old youth who was first seen when he was in the third week of a relapse of typhoid. During the week immediately prior to to the start of chloramphenicol therapy, the patient had had ten severe

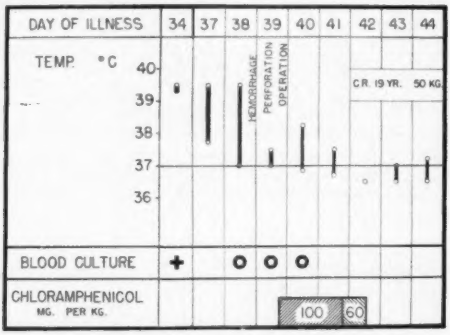

Chart 17.—This patient received chloramphenicol postoperatively after a course characterized by profuse epistaxes, high fever, intestinal hemorrhage and perforation. At operation gross soiling of the peritoneal cavity was observed. A large ileal perforation was repaired. No other drug therapy was administered. Significant improvement occurred forty-eight hours after the start of treatment, and convalescence was thereafter uneventful.

epistaxes, was in a constant delirium and had marked gross tremor of his extremities. On the eighteenth day of the relapse (thirty-eighth day of total illness) his temperature fell abruptly to 37 C. (98.6 F.), and he had a moderately large hemorrhage from the bowel. The following day the characteristic signs of a generalized peritonitis were present, and it was believed that an intestinal perforation had occurred. Accordingly, a laparotomy was performed, and a large perforation of the ileum near the cecum was found and repaired. The peritoneal cavity was grossly soiled with intestinal contents.

The administration of chloramphenicol was started one hour postoperatively, and the drug was given in aqueous suspension through a nasal tube placed in the stomach. No other antimicrobial therapy was administered.

Forty-eight hours after the operation (and start of antimicrobial therapy), there was no striking change in the patient's condition and he was still critically ill.

During the ensuing days, he recovered rapidly, however, and by the fifth post-operative day he was alert, completely rational, afebrile and hungry. The complete recovery was maintained thereafter.

Relapse: Clinical and bacteriologic relapse occurred in 4 of the 13 patients who received chloramphenicol. This incidence is comparable to the incidence of relapse in the aureomycin series and in the New York Hospital series of 46 untreated patients. The duration of the period between first defervescence and relapse was eight, sixteen, seventeen and nineteen days in the 4 patients receiving chloramphenicol, an interval similar to that seen in patients with untreated typhoid infections. One of the relapses occurred in a patient for whom antimicrobial therapy had been started early (sixth day) in the course of the illness. In the other 3 instances, however, antimicrobial therapy had been started on the twelfth to the eighteenth day of illness. Moreover, a high titer of antibody was present in these patients at the time of the relapse (table 5) and was of the same order as the titer in patients in whom no relapse occurred.

Three of the 4 patients with relapsing infections received chloramphenicol therapy for either seven or eight days, whereas relapse did not occurs in the patients treated for only sixty hours. This suggests that extension of the therapeutic regimen in an attempt to prevent relapse should be carried out considerably longer than the one week period. For the latter regimen may not be appreciably more efficient in this regard than forty-eight to sixty hours of treatment.

The administration of chloramphenicol was reinstituted in 2 of the 3 patients in relapse. In both of them recovery was prompt but followed a forty-eight hour lag period exactly as in the original treatment of the infection. In chart 14 may be seen the course of 1 of these patients. The remaining patient became acutely ill with high fever and prostration. Because of shortage of drug she was not retreated and made a gradual recovery after ten days of high fever and symptoms.

Course of Bacteremia During Chloramphenicol Therapy: Bacteremia was present in 8 patients at the time that use of chloramphenicol was started. As may be seen in chart 18, it was possible to isolate S. typhosa from the blood twenty hours after the initiation of therapy in 1 patient. Subsequent to this period, however, it was not possible to isolate bacilli from the blood of any of the patients who were receiving chemotherapy.

Comparison of Course of Bacteremia During Chloramphenicol and During Aureomycin Therapy: The inability to culture S. typhosa from the blood of patients receiving chloramphenicol is in striking contrast to the persistence of bacteremia for three days or more in an appreciable number of the patients who received aureomycin. These data may be seen in chart 18.

Comparison of the Mean Daily Temperatures of Patients Receiving Chloramphenicol and Receiving Aureomycin: In chart 19 may be seen a comparison of the mean daily temperatures of the patients in the chloramphenicol and aureomycin groups and similar observations in the

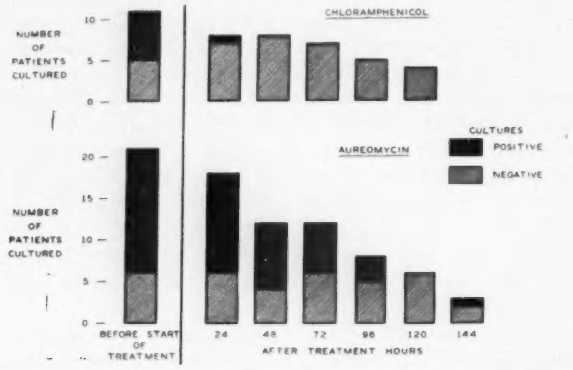

Chart 18.—Duration of S. typhosa bacteremia after chloramphenicol and aureomycin therapy. This comparison shows the virtually complete negativity of blood cultures after chloramphenicol therapy, in contrast to the continued presence of the organism for several days in the blood of patients receiving aureomycin.

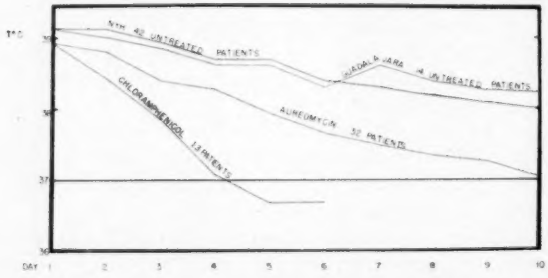

Chart 19.—Febrile course in typhoid fever. The figures at the botom of the chart indicate days of treatment or days in the hospital. The mean daily temperature of two untreated groups of patients corresponded closely during the first few hospital days. Aureomycin-treated patients had appreciably lower temperatures and returned more rapidly toward normal than did the untreated patients. Patients receiving chloramphenicol had prompt defervescence and by the fourth day mean temperatures were 37 C. or less. The relation of the temperature curves of these treated patients to those of patients receiving no therapy corresponds to the clinical opinion of the activity of the respective agents in this disease.

two previously described groups of untreated patients. The duration of the febrile illness before the period recorded in the graph was approxi-

mately the same for all four groups. All temperature determinations for each patient were averaged for each day (usually six) and the resulting values averaged for the four groups.

As may be seen in the chart, the curves for the two groups of untreated patients are virtually identical. Moreover, a significant difference exists between these curves and the curve for the aureomycin group. Nevertheless, the mean temperatures of the aureomycin-treated patients did not all attain normal values until nine days after the start of therapy. In contrast, the curve of the mean temperatures of the chloramphenicol-treated group fell rapidly and was within the normal range within seventy-two hours of the institution of therapy.

A comparison of the total duration of febrile illness for the four groups is presented in chart 10. In this chart the aureomycin series is subdivided into two groups according to the duration of illness at the time antimicrobial therapy was started. The day of admission to the hospital was arbitrarily designated as "start of treatment" for the two untreated series. As noted previously, the total febrile illness for the group which received early treatment with aureomycin is less than for the two untreated groups. The duration of febrile illness after the start of chloramphenicol therapy, however, was considerably less than for any other group, and this difference was statistically highly significant.

Miscellaneous Observations on Chloramphenicol, Aureomycin and Polymyxin B Groups.—Blood Culture in Diagnosis of Typhoid: S. typhosa was isolated by culture of the blood in 41 of the total group of patients with typhoid. In all but 11 instances the positive cultures were obtained on more than one occasion. It should be noted that in the patients from whose blood S. typhosa was not isolated, only one, or at the most two, blood cultures were obtained before therapy was begun. When duplicate cultures were made, it was observed that a higher percentage of positive cultures were obtained with the brain-heart medium. If these results are compared with those in table 1, describing the untreated patients with typhoid, it may be observed that the percentage of patients in whom positive cultures were obtained is almost the same.

Agglutination Reaction in Diagnosis and During Therapy: The course of the antibody titers during the chloramphenicol and aureomycin treatment of the infections may be seen in table 6. There was no apparent correlation between the titer of antibody and the presence of bacteremia. Moreover, there was no evidence that the development of antibodies was influenced by either chloramphenicol or aureomycin on the particular regimens used in the short period of post-treatment observation available.

Treatment of Chronic Carriers: The antimicrobial therapy of the chronic carrier state was studied in only 1 patient (E. M.), who had

been originally treated with polymyxin B. During the latter half of 1948 she received fortnightly courses of polymyxin B, aureomycin and chloramphenicol, all by the oral route. S. typhosa could not be cultured from fecal specimens during the administration of any one of these three drugs, but the bacilli invariably "returned" after the cessation of the antimicrobial therapy.

Stool Cultures in Typhoid: Twelve of seventy-nine stool cultures from patients receiving aureomycin or polymyxin B (2 patients, both with positive cultures) contained S. typhosa. Seven of these were obtained before treatment or on the first day of the drug therapy. Three were obtained during a relapse or convalescence. One each was obtained from patients who were receiving aureomycin for the second and sixth days, respectively. Moreover, it was regularly observed that little or no growth was obtained from stool specimens taken after twenty-four hours of aureomycin treatment had been administered. Subsequently, however, proteus organisms appeared and were obtained from almost all cultures taken late in the period of aureomycin treatment.

The twelve positive stool cultures were obtained from 10 different patients. At that time 34 patients with typhoid were being followed, and the percentage of patients with positive cultures would then be 29. This is appreciably lower than that observed in the New York Hospital patients and may represent an effect of aureomycin (given to 32 of the 34 patients) on the typhoid organisms in the stool.

None of the patients receiving chloramphenicol showed positive stool cultures during the time of treatment; however, 2 patients were reported to be carriers after an apparent arrest of their disease with this therapy.

Toxicity: The toxic reactions observed during the administration of polymyxin B have already been described.

There were no serious manifestations of toxicity noted during the administration of aureomycin. In approximately half of the patients, nausea, vomiting and occasionally diarrhea occurred while they were receiving this drug. In no instance was it necessary to discontinue the use of aureomycin because of these gastrointestinal reactions, despite the fact that all the patients were acutely ill with a disease in which gastrointestinal manifestations are prominent.

Within the dose range of 4 to 25 Gm. daily for adult patients, there did not appear to be any particular correlation between the size of the daily dose and the occurrence of nausea and vomiting. The range of dose related to body weight for the entire aureomycin-treated series was 47 to 500 mg. per kilogram.

The administration of chloramphenicol in daily doses as high as 100 mg. per kilogram of body weight was not associated with either serious toxicity or gastrointestinal disorders.

TABLE 6.—*Bacteremia and Antibody Titer (Widal Test) in Patients with Typhoid*

Patient	S. Typhosa Bacteremia	Widal Antigen	Weeks After Onset *								
			1	2	3	4	5	6	7	8	9
Treated with Polymyxin B											
G. W.	+	H		2,560	5,120	2,560		640			
		O		640	1,280	1,280		1,280			
E. M.	+	H		40	40						
		O		160	160						
P. P.	+	H									
		O	Not done								
C. G.	+	H					0	320	80		320
		O					0	160	80		80
Treated with Aureomycin											
T. Ro.	0	H	0		0						
		O	160		160						
L. Cr.	+	H		0	0						
		O		40	80						
R. Ur.	+	H	0	0		0					
		O	160	160		160					
R. Vl.	+	H	20	160							
		O	160	640							
G. Lu.	+	H		0	0						
		O		160	320						
H. To.	0	H		0		320					
		O		160		160					
A. Ur.	0	H		40	160		160				
		O		80	160		320				
E. B.	+	H									
		O	Not done								
F. Me.	0	H		1,280	320						
		O		160	640						
N. Ca.	0	H		640	160						
		O		320	160						
L. Gom.	+	H		160	160	1,280					
		O		320	1,280	640					
E. Pa.	0	H		80	320	80					
		O		80	160	160					
J. C.	+	H	80			160			320		
(N. Y.)		O	640			320			1,280		
P. Al.	+	H	40	320	640						
		O	320	320	320						
E. Gz.	+	H	80	160		320		320			
		O	40	160		80		80			
G. Ma.	+	H		0	0	80					
		O		20	20	40					
A. Del.	+	H		1,280	2,560						
		O		1,280	5,120						
H. Va.	+	H			0	40				0	
		O			320	320				320	
J. Ro.	0	H		80	160						
		O		320	320						
C. Ga.	0	H			160	160	320				
		O			160	640	320				
A. G.	+	H		640							
(N. Y.)		O		1,280							
G. Bo.	+	H		80	320	80					
		O		80	160	160					
J. Bo.	+	H			160	320					
		O			80	160					
E. Mo.	+	H			2,560	640					
		O			2,560	1,280					
G. W.	+	H									
		O	(See under polymyxin B)								
L. B.	+	H				2,560					
		O				2,560					
Ca. B.	+	H			80	160		640			
		O			160	160		640			
J. Ur.	0	H				160	160	160			
		O				20	80	40			
N. Mas.	+	H				640	320				
		O				320	320				

* The figures designate dilutions (1:2,560, etc.).

TABLE 6.—*Bacteremia and Antibody Titer (Widal Test) in Patients with Typhoid—Continued*

Patient	S. Typhosa Bacteremia	Widal Antigen	Weeks After Onset * 1	2	3	4	5	6	7	8	9
C. Re.	+	H				1,280	2,560				
		O				1,280	2,560				
H. R.	+	H				2,560	5,120				
		O				2,560	2,560				
J. R.	+	H				5,120	2,560				
		O				2,560	2,560				
E. Ca.	+	H								320	
		O								320	
Ja. Ur.	+	H				320	320				
		O				160	40				
			Treated with Chloramphenicol								
J. Go.	+	H									
		O	Not done								
G. C.	+	H	0	160							
		O	40	640							
G. Lu.	+	H	600								
		O	160								
H. Ro.	+	H		160		320					
(N. Y.)		O		640		1,280					
L. Ru.	0	H		0	0	0					
		O		80	80	160					
A. Si.	+	H		0	0						
(N. Y.)		O		320	160						
D. C.	±	H					...				
(P. R.)		O					800				
N. G.	+	H			1,280	1,280					
		O			640	640					
Y. Mi.	+	H		1,600	1,600						
(N. Y.)		O		40	400						
A. Lo.	+	H			400						
		O			100						
M. Ro.	+	H			80	160					
		O			160	640					
		O 1				40	320	80			
G. He.	+	H				40	160	160			
C. R.	+	H					160				
		O					640				

* The figures designate dilutions (1:1,280, etc.).

On the highest doses used (100 mg. per kilogram), the peak concentration of chloramphenicol in the serum was usually about 100 micrograms per cubic centimeter. The administration of aureomycin in a single dose of 50 mg. per kilogram (determined on normal persons in this laboratory) has usually been followed by peak concentrations which ranged between 5.0 and 6.25 micrograms per cubic centimeter.

Previous Immunization: A history of previous immunization against typhoid was obtained from only 2 of the entire series of patients with typhoid. Both of these previously immunized persons were in the aureomycin group. In each instance the diagnosis was made by the demonstration of S. typhosa bacteremia. The interval between immunization and infection was sixteen months in 1 case and four years in the other. The clinical disease experienced by these 2 previously immunized patients was not conspicuously different from that suffered by the other patients.

A history of previous typhoid infection was not obtained from any patient in the entire series.

COMMENT

The range of the severity and duration of individual cases of typhoid varies considerably and is particularly variable after the first two weeks of illness. The age of the patient is also of importance in determining severity, for the infection is not usually severe during infancy and is notably severe in adolescence and middle age. Abrupt recovery from typhoid is infrequent but may occur, particularly during the fourth week of illness. In general, the persistence of bacteremia or the recent development of the cutaneous eruption are indications that abrupt recovery is not imminent. Moreover, in most persons recovery is gradual and the disease persists for approximately one month. Nevertheless, the individual variation in the length and severity of typhoid infections is sufficiently great to render difficult the evaluation of antimicrobial agents in this disease. Consequently, in typhoid, as in other infections of a variable course, the most satisfactory criterion for measuring the effect of a therapeutic agent is the uniformity with which its use is followed by an impressive change in the course of the infection.

In the present series of 51 patients with typhoid, the administration of chloramphenicol was followed by recovery within seventy-two hours of all 13 patients treated. Aureomycin appeared to exert some effect, especially on the course of early infections. Nevertheless, the course of the disease following the use of aureomycin was not uniform and the effects were frequently negligible. The administration of polymyxin B failed to influence the course of the disease in any way.

The uniformity with which recovery occurred after the administration of chloramphenicol in the present series of patients with typhoid is in complete agreement with the results previously reported by Woodward, Smadel and their associates.[9] In a preliminary report, these investigators presented the relevant data on 11 cases of bacteremic typhoid in all of which chloramphenicol had been started on or about the tenth day of illness. In every instance it was impossible to isolate S. typhosa from the blood once treatment had been started, and defervescence with symptomatic recovery occurred within an average period of seventy-two hours from the first administration of the drug. In 1 of their patients intestinal hemorrhage and perforation occurred a few hours after completion of the initial defervescence, but with continuation of the antimicrobial therapy recovery was uneventful.

In the present study, recovery occurred in a desperately ill man who had experienced an intestinal hemorrhage and perforation before chloramphenicol was started. Moreover, it was also impossible to cul-

9. Woodward, T. E.; Smadel, J. E.; Ley, H. L., Jr.; Green, R., and Mankikar, D. S.: Preliminary Report on the Beneficial Effect of Chloromycetin in the Treatment of Typhoid Fever, Ann. Int. Med. **29**:131-134, 1948.

ture S. typhosa from the blood of patients who had received chloramphenicol for more than twenty hours.

The question immediately arises as to whether the bacteremia was truly "reversed" after use of chloramphenicol or whether the bacilli were permanently inhibited during incubation of the blood culture itself by the chloramphenicol present in the specimen. This possibility could be operative only in the case of chloramphenicol, for aureomycin is rapidly inactivated when incubated in the presence of blood. In the absence of a chloramphenicol inactivator which could be used in the cultures, it is impossible to answer this question with certainty. To be sure, in many instances in the present study, the chloramphenicol in the blood culture flasks would be diluted by the medium to a concentration appreciably below the amount necessary for the inhibition of S. typhosa in vitro. Such observations are by no means conclusive, however, because nothing is known concerning the effect of subinhibitory concentrations of chloramphenicol on typhoid bacilli which have previously experienced some exposure to the drug in vivo. The principal reason, however, for assuming that the sterile blood cultures during treatment with chloramphenicol represent disappearance of bacteremia is the fact that the finding is uniformly followed (twenty-four hours later) by a remission of all clinical evidences of infection.

Thus, the results observed from the use of chloramphenicol in these patients were identical with those reported by Woodward and his associates. In addition, in the present study a deliberate attempt was made to include some cases of more than ten to twelve days' duration. This was done because of the possibility that the early bacteremic cases of typhoid might be more susceptible to antimicrobial therapy than the severe protracted infections. In the latter type of case it was considered possible that a part of the total illness might represent a response of the host to accumulated endotoxins rather than active bacterial metabolism per se. In the 9 infections of thirteen to thirty-nine days' duration, however, the response to the administration of chloramphenicol was almost as rapid and complete as in all but the case of only six days' duration. It should be emphasized that in these late cases the patients were all seriously ill and presented no indications that the processes of natural recovery were becoming operative.

There was very little overlapping between the most rapid recoveries seen during the administration of aureomycin and the least rapid recovery observed following the use of chloramphenicol. Only 2 of the patients who received aureomycin recovered as rapidly as any of those receiving chloramphenicol. Moreover, as mentioned previously, one of the rapid recoveries due to aureomycin occurred in a patient of an age (3 years) at which typhoid is not usually severe and whose small size permitted the administration of 500 mg. of aureomycin per kilogram

of body weight. Furthermore, bacteremia persisted for several days in an appreciable number of patients, although in no instance did it persist throughout the entire period of aureomycin therapy. Interpretation of the latter fact is rendered difficult, however, because the bacteremia of typhoid may disappear naturally before there is any indication that the patient is recovering. The incidence of relapse (7 in 34 cases) in the aureomycin series cannot be considered to provide indirect evidence of drug activity (i. e., by interfering with the usual development of immunity), for both the incidence of relapses and the time of their appearance were essentially the same as in the untreated group.

Thus, the case in favor of a beneficial action of aureomycin in typhoid rests on the short duration of total illness in patients treated on or before the twelfth day of illness and the fact that no complications were observed in any of the surviving patients. Neither of these findings is conclusive, and both are much less impressive than the uniformly abrupt recovery seen during the administration of chloramphenicol. On the basis of the observations presented, however, it is reasonable to believe that aureomycin does exert an effect on the course of typhoid but that the effect so exerted is by no means as great as the effect produced by the administration of chloramphenicol.

It is conceivable that a period of powerful antimicrobial therapy which failed to eradicate the infection might suppress or delay the natural acquisition of immunity. In such a situation it would be anticipated that the incidence or relapse would be increased and the interval between defervescence and relapse would be appreciably shortened. Support for these suppositions was not obtained from the results in the present small chloramphenicol series. Despite the apparently powerful effect of this drug on the acute illness, the incidence of relapse after its use was the same as in the aureomycin series or in the patient with untreated typhoid. It is possible, therefore, that the initial recovery observed during the administration of chloramphenicol is attained without compromising the usual development of the forces of natural immunity.

It is probable that the action of chloramphenicol in typhoid, like that of drugs used in the treatment of most other infections, is limited to checking the onward progress of the infection until final control can be effected by the mobilization of the immune forces of the host. If this is true, in order to reduce the incidence of relapse in typhoid to a minimum, it would be necessary to continue the administration of chloramphenicol until the defense forces of the host had become maximally operative. The length of the period required for such maximal mobilization is not known, but from the average duration of febrile illness in untreated patients it would appear to be three to four weeks. It might be presumed, therefore, that it would be advisable to continue the administration of chloramphenicol in typhoid for a

period almost as long as that usually required for natural recovery. It is of interest in this connection that one of the relapses in the present chloramphenicol-treated patients occurred twenty-six days after the start of antimicrobial therapy.

An alternative to the long-continued antimicrobial therapy of typhoid fever would be to treat each patient only until the onset of defervescence. Subsequent relapses could then be retreated as they occurred or a second short course of chloramphenicol could be administered at an arbitrarily chosen period during the third or fourth week after the beginning of the illness. This two course system has been successfully used by Smadel, Woodward and their associates in the management of the relapses which may occur following the short term chloramphenicol treatment of scrub typhus produced in human volunteers.[10] (Relapses in such infections are presumably a consequence of interference with the development of immunity in the host by the unusually early antimicrobial therapy of the experimental infection. Relapse following chloramphenicol treatment of naturally acquired scrub typhus has not been observed.)

There are two reasons that it is inadvisable to adapt this short term therapy to the treatment of typhoid with chloramphenicol. First, although there is no evidence as yet that a short course of the drug interferes with the development of immunity and hence increases the possibility of relapse, the total number of patients treated is too small to be certain of the point. Secondly, unlike scrub typhus, in which the onset of recovery is almost immediate, in typhoid the forty-eight hour lag in the onset of recovery may occur during the chloramphenicol treatment of a relapse as well as during the treatment of the initial illness (chart 14). A regimen of therapy which would include such a forty-eight hour period of acute illness as an accepted risk for some patients has obvious disadvantages. For these reasons, it appears that the most satisfactory procedure in the chloramphenicol treatment of typhoid would be to continue therapy for a period sufficient for the host to become enabled to exert final control of the infection. Evidence on this point has recently been reported by Smadel and his co-workers,[11] who encountered no relapses in a series of 31 patients treated with chloramphenicol for periods ranging from nine to twenty-three days. Since more than half of this group received treatment for fourteen days or less, they felt that there was little advantage to be gained in continuing treatment for more than two weeks.

10. Woodward, T. E.; Ley, H. L., Jr., and Smadel, J. E.: The Chemoprophylasis of Scrub Typhus in Volunteers, J. Clin. Investigation **28**:819-820, 1949.

11. Smadel, J. E.; Woodward, T. E., and Bailey, C. A.: Relation of Relapses in Typhoid Fever to Duration of Chloramphenicol Treatments, J. A. M. A. **141**: 129 (Sept. 10) 1949.

In the present study, no attempt was made to determine the minimal effective dose of chloramphenicol. The practice of substantially reducing the daily dose once defervescence had occurred appeared to be satisfactory. Consequently, at present it appears advisable to administer approximately 100 mg. of chloramphenicol per kilogram of body weight (i. e., 5 to 7 Gm. in an adult) each day while the patient remains acutely febrile and to reduce the total daily dose to 25 mg. per kilogram (1 to 2 Gm.) on the third or fourth day of illness when defervescence has occurred. Seven grams daily provides satisfactory serum concentrations of the drug in even large patients, and there is probably no reason to exceed this dosage even in persons weighing more than 70 Kg. The use of this fourteen day regimen would require approximately 32 Gm. of chloramphenicol for 70 Kg. (154 pound) patient.

The forty-eight hour lag before the first appearance of clinical improvement is a most striking phenomenon in the chloramphenicol treatment of typhoid. The phenomenon was observed in all patients of the present study, save for the young boy for whom treatment was started on only the sixth day of illness. During the first two days of chloramphenicol treatment of the other patients, there was not the slightest indication that the drug was influencing the course of the infection. Then during the third day of treatment the first signs of improvement would appear, and the process of recovery would be completed with dramatic suddenness. The speed with which defervescence appeared and the completeness of the rapid disappearance of the other manifestations of infection justify the use of the term "crisis" to describe the phenomenon.

The mechanism of this forty-eight hour lag before the onset of crisis is an intriguing subject for speculation. Typhoid differs from certain other bacterial infections, such as pneumococcus pneumonia, in two important particulars. First, as shown by Goodpasture,[12] the micro-organisms are situated within monocytes and plasma cells. Second, the micro-organisms produce a potent endotoxin which circulates through the body and which is capable of producing in rabbits an illness resembling in many particulars the disease as it occurs in man.[13]

In general, if it can be demonstrated that a particular drug is capable of exerting powerful antimicrobial activity in vivo against some infections, the drug will be similarly effective in vivo against all bacterial species which are inhibited by low concentrations of the drug in vitro. Such is not the case, however, with typhoid or with tuberculosis or brucellosis, the other frequently encountered intracellular bacterial

12. Goodpasture, E. W.: Concerning the Pathogenesis of Typhoid Fever, Am. J. Path. **13**:175-185, 1937.

13. Morgan, H. R.: Pathologic Changes Produced in Rabbits by a Toxic Somatic Antigen Derived from Eberthella Typhosa, Am. J. Path. **19**:135-143, 1943.

infections. The causative agents of these three diseases are inhibited in vitro by low concentrations of a number of drugs of proved value in the treatment of other infections; yet only a very few of these drugs are conspicuously effective against typhoid, tuberculosis or brucellosis in vivo. For example, streptomycin and aureomycin, two potent antimicrobial agents, inhibit S. typhosa in vitro in concentrations comparable (on a weight basis) to the antityphoid inhibitory concentrations of chloramphenicol, yet are notably ineffective, or much less effective, than chloramphenicol in the treatment of typhoid.

In any consideration of the mechanics of the antityphoidal action of chloramphenicol, it is only proper that these important characteristics of the disease itself receive attention. Accordingly, it would seem that the forty-eight hour lag before the onset of crisis during chloramphenicol might be a consequence of one of four possibilities: (1) approximately forty-eight hours might be required for the attainment of proper concentrations of chloramphenicol at the sites of most active infection; (2) assuming the rapid accumulation of drug at the lesion, forty-eight hours might be required for the inhibition of a significant number of parasites by the drug or certain forces of the host; (3) the intracellular situation of a large proportion of the parasites might protect them from contact with the drug or host defenses, or (4) the micro-organisms might be rapidly affected by the drug, but approximately forty-eight hours might be necessary for the removal of endotoxin which either had been liberated in the process or had accumulated previous to the antimicrobial therapy.

Chloramphenicol is rapidly absorbed from the gastrointestinal tract, and high concentrations of the active form of the drug are speedily attained in the blood and presumably also in the extracellular fluid. Moreover, when S. typhosa is growing extracellularly in vitro, the action of chloramphenicol is speedily manifested and the major part of the bacterial population is inhibited within twelve hours. Furthermore, in the disease in human patients, bacteremia is apparently (though not certainly) reversed within a few hours of the start of therapy, thus indicating that the antityphoidal activity of chloramphenicol becomes operative soon after the drug therapy is started. As a consequence, it is distinctly unlikely that either of the first two possibilities listed in the preceding paragraph plays a significant role in producing the delay in the appearance of clinical improvement.

Information concerning the importance of the intracellular situation of the bacillus is less definite. It certainly cannot be denied that if chloramphenicol has the property of penetrating monocytes and plasma cells the attainment of appropriate inhibitory concentrations of the drug within these cells might require considerably more time than the attainment of such concentrations in the extracellular fluid. Moreover, the alternative

notion that typhoid bacilli situated within these cells would be protected from contact with chloramphenicol is undeniably attractive. In order to explain the forty-eight hour lag period on the basis of the latter supposition, however, it would be necessary to make one of two further assumptions: (1) that within any forty-eight hour period a significant number of the intracellularly situated bacilli become vulnerable to the drug, possibly by leaving the protection of the cell, or (2) that in order to produce crisis it is necessary only to interfere with the metabolic activities of the infecting population which is existing intracellularly.

It is obviously impossible to affirm or deny that the intracellular situation of S. typhosa does not protect the micro-organisms from the contact with the drug and hence play an important role in the production of the forty-eight hour lag phenomenon. Nevertheless, strong evidence against the validity of this notion is afforded by the fact that in the chloramphenicol treatment of two other predominantly intracellular infections, brucellosis and typhus, a forty-eight hour lag does not usually occur before the onset of recovery.

This particular type of evidence requires qualification in one respect. The type of host cell principally involved by typhus, typhoid and brucellosis is not the same in all three diseases (vascular endothelium in typhus, monocyte in brucellosis, plasma cell and monocyte in typhoid). Moreover, aureomycin, which is notably effective against two of these predominantly intracellular infections, is relatively ineffective against typhoid, despite the fact that the antityphoidal activity in vitro is comparable to that of chloramphenicol. Thus, the possibility cannot be excluded that it is the plasma cell in particular and not just any intracellular situation of the parasites which is unique in typhoid.

Other than this possibility that there are significant factors unique to the plasma cell, the most likely explanation for the forty-eight hour lag period on the basis of present knowledge is that it reflects the period necessary for the disposal of significant quantities of endotoxin.

Quantitative studies on the rates of formation and disposal of endotoxin during the course of typhoid are not available. It has been amply demonstrated, however, that only minute amounts of purified material [14] (i. e., 2 micrograms) will produce acute reactions in susceptible subjects and that the tolerance which is acquired by frequently repeated injections of the material can always be overcome if a sufficiently large dose is used. The quantities of endotoxin usually produced during a single day of typhoid may be rapidly excreted or neutralized. It is reasonable to believe, however, that an appreciably larger amount of endotoxin would be released during the sudden inhibition and subsequent death of a significant portion of the bacterial population as a

14. Morgan, H. R.: Resistance to the Action of the Endotoxins of Enteric Bacilli in Man, J. Clin. Investigation **27**:706-709, 1948.

consequence of the action of chloramphenicol. In such situations, the onset of crisis might well be postponed for the forty-eight hour period usually observed in the patients.

The fact that recovery was sustained in the bacteremic patient who received therapy only up to the onset of crisis affords some support for the notion that the forty-eight hour lag period represents delay in the disposal of endotoxin. If the lag before the onset of crisis represented a period necessary for proper accumulation of chloramphenicol or for the initiation of its action, it would be anticipated that if the administration of the drug were stopped just as its full activity were becoming operative, only a transient beneficial effect would occur in the course of the infection.

From this consideration of the many factors which are conceivably involved, it seems likely that the antimicrobial action of chloramphenicol becomes operative soon after the first administration of the drug and that the forty-eight hour lag phenomenon, which seems to be unique in typhoid fever, represents a period necessary for the disposal of endotoxin.

Regardless of the true nature of the mechanism, the speed with which crisis may occur in some patients is sufficiently rapid so that it would seem advisable to observe patients carefully during this period for possible evidences of the onset of peripheral circulatory collapse. Moreover, as Woodward has emphasized,[9] risk of the anatomic complications of intestinal hemorrhage or perforation continues for at least several days after the crisis.

Chloramphenicol is vastly superior to aureomycin in the treatment of typhoid (and presumably the other Salmonella infections), whereas the two drugs have essentially comparable activities in all other infections susceptible to either. This unique effectiveness in typhoid cannot be explained merely on the basis of a quantitative difference in antimicrobial activity between the two drugs, such as exists, for example, between sulfanilamide and sulfadiazine. Nor is it reasonable to believe that the phenomenon is a consequence of the definite differences in the absorption of the two drugs from the gastrointestinal tract. If either of these situations obtained, it would have to be assumed (*a*) that typhoid, brucellosis and the rickettsial infections were all affected by a chemical component common to the two drugs but more readily available in chloramphenicol, and (*b*) that higher concentrations of the substance in question are necessary for the inhibition of S. typhosa in vivo than is the case for the other two disease-producing agents. If these essentially quantitative differences were the determining factor in the different antityphoidal activities of the two drugs, it should follow that chloramphenicol would also be more active than aureomycin in the treatment of brucellosis. In actuality, however, such is not the case.

In a study by us, published elsewhere,[15] it was observed that chloramphenicol was definitely no more active (on a weight basis) than aureomycin in the treatment of brucellosis and possibly was slightly less active.

Thus it appears that the marked difference in the antityphoidal activities of chloramphenicol and aureomycin is not merely a quantitative phenomenon but is a consequence of factors unique either to the lesions of typhoid or to S. typhosa itself.

The factors of possible significance in the lesions of typhoid have already been discussed, and any difference between chloramphenicol and aureomycin in regard to these factors (e. g., penetration of plasma cells) might explain the difference in the effectiveness of the two drugs.

In regard to possible factors unique to the parasite itself, it is worthy of mention that Salmonella display a notable degree of discrimination in their relative avidities for the individual members of another series of antimicrobial drugs. Rake and his associates[16] have observed that Salmonella are unique among a large number of bacterial species studied in respect to the action of streptomycin and its derivatives. Four compounds were studied: streptomycin, mannosidostreptomycin, and the respective dihydro derivatives of each. Streptomycin and dihydrostreptomycin exerted nearly identical (on a weight basis) degrees of activity in vitro against all sixteen bacterial strains tested except for the strains of S. typhosa and Salmonella schottmuelleri, against which the activity of streptomycin was four to five times that of the dihydro derivative. In contrast, the two mannosido compounds were in general only one fourth to one seventh as active as streptomycin against the various bacterial species tested, again with the exception of the two strains of Salmonella, against which both compounds nearly equaled the activity of streptomycin and exceeded that of dihydrostreptomycin.

Hobby has also observed that significant differences among the various streptomycins can be demonstrated by comparing their activities against Salmonella.[17] It is evident, therefore, that Salmonella are much more sensitive to changes in the structure of at least one series of antimicrobial agents than are the other bacterial species which commonly produce disease in man.

From the observations of the present study, which are in agreement with the previous observations of Woodward and his associates, it

15. Knight, V.; Ruiz-Sanchez, F., and McDermott, W.: Chloramphenicol in the Treatment of the Acute Manifestations of Brucellosis, to be published.

16. Rake, G.; Pansy, F. E.; Jambor, W. P., and Donovick, R.: Further Studies on the Dihydrostreptomycins, Am. Rev. Tuberc. **58**:479-486, 1948.

17. Hobby, G. L., and Lenert, T. F.: Biological Activity of a Residual Form of Streptomycin Against Eberthella Typhosa, Proc. Soc. Exper. Biol. & Med. **65**: 249-254, 1947.

appears that chloramphenicol is distinctly superior to aureomycin in the treatment of typhoid but that this superiority does not extend to many other infections such as typhus or brucellosis.

It is possible that further studies of these phenomena (relative inefficacy of aureomycin, lag before onset of crisis following administration of chloramphenicol) which are essentially peculiar to typhoid might provide important information concerning the mechanics of the host-parasite-drug relation in this and other intracellular bacterial infections.

SUMMARY

An investigation of the antimicrobial therapy of typhoid has been conducted in 50 patients (51 cases) who were all acutely ill with the disease. The administration of polymyxin B to 4 patients resulted in no beneficial effects definitely attributable to the drug and was accompanied with serious manifestations of toxicity. Thirty-one of 34 patients who received aureomycin made uncomplicated recoveries and it was possible to show that the duration of total illness in patients who received treatment early in the infection was reduced. The results were not uniform, however, and frequently were negligible; hence it is not possible to attribute them with certainty to the action of the drug.

All of 13 patients who received chloramphenicol recovered promptly within approximately seventy-two hours, regardless of the severity or the duration of the infection when antimicrobial therapy was started. This marked superiority of chloramphenicol over aureomycin is virtually unique to typhoid and was not observed in a concurrent study of the two drugs in the treatment of brucellosis and rickettsial infections.

A NEW SULFONAMIDE (GANTRISIN®)

Studies on Solubility, Absorption and Excretion

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CHICAGO

A NEW compound, 3,4-dimethyl-5-sulfanilamido-isoxazole (gantrisin®), appears to show considerable promise as an effective sulfonamide; so far in our hands it has produced no renal complications. The antibacterial and clinical effectiveness of this compound has been reported on by Schnitzer and others,[1] Sarnoff and others,[2] Lazarus,[3] Rhoads and others,[4] Haines and Miceli,[5] Narins [6] and Rodgers and Colby.[7] It was found by these workers to compare favorably with other commonly used sulfonamides. Their results indicated that it is effective

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This compound, prepared and supplied by Hoffman-LaRoche, Inc., Nutley, N. J., was formerly known as NU 445.

1. Schnitzer, R. J.; Foster, R. H. K.; Ercoli, N.; Soo-Hoo, G.; Mangieri, C. N., and Roe, M. D.: Pharmacological and Chemotherapeutic Properties of 3, 4-Dimethyl-5-Sulfanilamido-Isoxazole, J. Pharmacol. & Exper. Therap. **88**:47-57 (Sept.) 1946.

2. Sarnoff, S. J.; Freedman, M. A., and Hyman, A. A.: Treatment of Bacillus Proteus Infections with Nu-445, J. Urol. **55**:417-427 (April) 1946.

3. Lazarus, J. A.: Suggestions Regarding Management of Severely Affected Kidneys, M. Clin. North America **32**:1415-1425 (Sept.) 1948.

4. Rhoads, P. S.; Svec, F. A., and Rohr, J. H.: Clinical Evaluation of a New Sulfonamide—Gantrisin, Quart. Bull., Northwestern Univ. M. School **23**:104-111, 1949.

5. Haines, W. H., and Miceli, S.: Some Observations on the Management of B. Proteus Infections of the Urinary Tract, Pennsylvania M. J. **50**:1328-1330 (Sept.) 1947.

6. Narins, L.: The Treatment of Bacillus Coli and Bacillus Proteus Infections of the Urinary Tract with a New Sulfonamide (Nu-445), J. Urol. **59**:92-95 (Jan.) 1948.

7. Rodgers, R. S., and Colby, F. H.: A Clinical Evaluation of a Recent Sulfonamide: Nu-445, J. Urol. **59**:659-663 (April) 1948.

in the treatment of infections of the urinary tract, especially those caused by Escherichia coli. It has also been found to be moderately effective against Proteus. It has been used as the sole bacteriostatic agent in 10 cases of meningococcic meningitis [4] with complete recovery.

The toxic manifestations encountered have been similar in nature to those produced with other sulfonamides with the exception of the absence of renal complications. Narins [6] treated 50 patients with 6 to 8 Gm. of gantrisin* daily for six to sixty days and reported 2 instances each of dermatitis and nausea. In a series of 91 cases reported by us there were 9 reactions with 2 episodes of crystalluria which disappeared while the sulfonamide therapy was being continued. To the time of writing, we have used the drug in the treatment of 300 patients, without any evidence of renal damage, even though alkali therapy was seldom used. In order more fully to evaluate the merits of gantrisin,* studies were made on solubility, absorption and excretion. The compound was supplied in the oral tablet form and as a 40 per cent solution of the ethanolamine or diethanolamine salt for intravenous and intramuscular administration.

SOLUBILITY AS COMPARED WITH SULFADIAZINE

The solubility of gantrisin,* sulfadiazine and their acetyl forms in urine was determined as follows: At room temperature (24 to 25 C.) an excess of the powdered compound to be dissolved was placed in aliquots of normal twenty-four hour urine excretions. The p_H was determined with a Leeds and Northrup glass electrode p_H meter and adjusted to the desired hydrogen ion concentration by addition of tenth-normal sodium hydroxide solution or hydrochloric acid. The mixture was shaken at intervals for thirty minutes and filtered through a Whatman no. 40 filter paper. The first 2 to 3 cc. was discarded to insure a clear filtrate. The final p_H reading was made on this filtrate and the concentrations of the dissolved material determined according to a slight modification of the method of Bratton and Marshall.[8] It was found that the filtrate showed no appreciable change in the solubility on standing up to twenty-four hours; hence, thirty minutes was selected as the time interval for saturation to take place.

The results are shown in chart 1. The solubility of gantrisin* rapidly increases from 60 mg. per hundred cubic centimeters at p_H 5.4 to 327 mg. per hundred cubic centimeters at p_H 6.14, whereas the solubility of sulfadiazine at p_H 6.3 is only 12.9 mg. per hundred cubic

8. Bratton, A. C., and Marshall, E. K., Jr.: A New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:537-550 (May) 1939.

centimeters. The solubility of sulfadiazine approaches that of gantrisin® only after the p_H of the urine is raised to 7.5 or 8. The free form of gantrisin® is more soluble than the acetylated form up to p_H 6.6, whereas the opposite is true of sulfadiazine. About 70 per cent of the excreted gantrisin® is in the free form, which is the most soluble fraction.

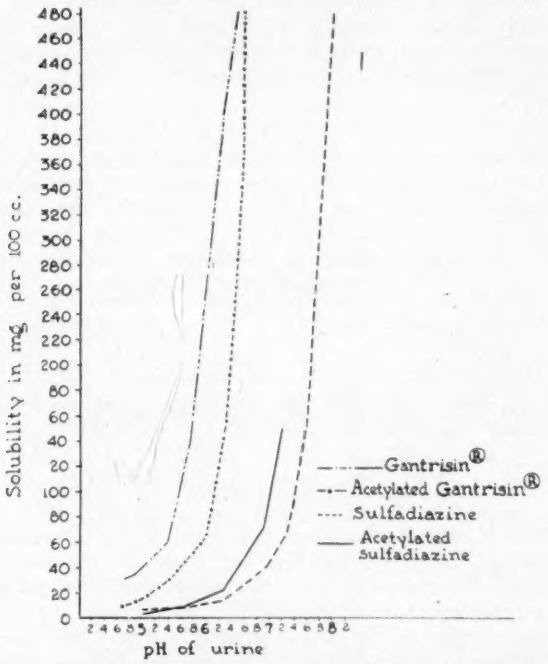

Chart 1.—Comparative solubility of gantrisin®, sulfadiazine and their acetylated derivatives in normal urine at various p_H levels.

DOSAGE

Oral and intramuscular administration was in 1 or 1.5 Gm. doses every four hours, day and night. In a few instances 2 Gm. was given every four hours. When the drug was given intravenously, the dosage was usually 2 Gm. every eight hours. It was injected directly into the vein in a period of one to two minutes in some cases. In others, it was given slowly in 1 liter of 5 per cent glucose solution or in isotonic saline solution. Up to 12 Gm. per day has been given in some instances without any untoward effect.

Ten patients received intramuscular injections of the 40 per cent solution of the ethanolamine salt of gantrisin,® 1 Gm. every four hours for two to three days, and 2 patients received a 40 per cent solution of the diethanolamine salt of gantrisin® in a similar manner. Twelve patients received a similar amount of the 40 per cent solution of ethanolamine salt intravenously in fluids, and 7 patients were given the 40 per cent solution of diethanolamine salt. Single initial doses up to 4 Gm. occasionally were given directly into the vein when a quick high level was desired, as in the treatment of bacterial meningitis. No untoward reactions were noted from the intramuscular or intravenous use of gantrisin.®

ABSORPTION AND EXCRETION

Blood levels produced by a uniform dosage of gantrisin® (1 Gm. every four hours orally, intravenously or intramuscularly) were determined, as well as twenty-four hour urinary excretions. The amount of

TABLE 1.—*Average Levels of Gantrisin® in Blood and Urine of Patients Receiving 6 Gm. Daily*

	Blood					Urine				
Administration	Determinations	Patients	Free Form, Mg./100 Cc.	Total, Mg./100 Cc.	Conjugated (Acetylated) Form, per Cent	Determinations	Patients	Free Form, Gm./24 Hr.	Total, Gm./24 Hr.	Conjugated (Acetylated) Form, per Cent
Oral	22	10	5.85	9.17	35	16	8	2.23	3.61	35
Intravenous	14	11	11.7	16.7	30	9	8	2.6	3.77	31
Intramuscular	19	8	6.67	9.29	28	12	8	2.67	4.12	35

the drug that was conjugated was determined by subtracting the concentration of the free form from that of the total. The results are shown in table 1. The levels shown are those determined on blood samples drawn the morning after administration of several doses of the drug at four hour intervals and just prior to giving the next four hour dose of the drug. Higher levels probably existed at some time during the four hour period previous to the drawing of the blood.

The highest blood levels, averaging 11.7 mg. per hundred cubic centimeters of the free form and 16.7 mg. per hundred cubic centimeters total, were obtained when the drug was given intravenously. The next highest levels, 6.61 mg. per hundred cubic centimeters free and 9.29 mg. per hundred cubic centimeters total, were obtained when it was given intramuscularly. The lowest levels, 5.85 mg. per hundred cubic centimeters free and 9.17 mg. per hundred cubic centimeters total, were obtained with oral administration.

The acetylated portion varied between 28 and 35 per cent and was about the same in the urine as in the blood. The route of administra-

tion had very little effect on the degree of acetylation. The average total amount of the drug excreted during a twenty-four hour period was likewise similar for all three methods of administration, varying between 3.61 and 4.12 Gm. on an intake of 6 Gm., with an average of 3.85 Gm. excreted in twenty-four hours. Assuming that 1,500 cc. of urine was excreted during a twenty-four hour period, this represents a urinary concentration of 257 mg. per hundred cubic centimeters.

Since the solubility of gantrisin® is such that a concentration of 265 mg. per hundred cubic centimeters is present in normal urine at p_H 6.06, it would appear that there would be relatively little danger of crystalluria at p_H 6, whereas sulfadiazine does not approach this solubility until the p_H of the urine is above 7.6.

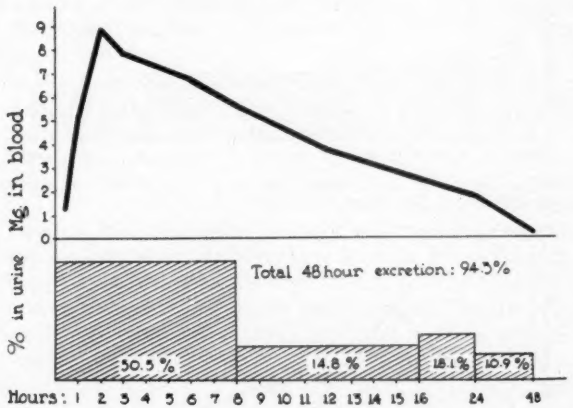

Chart 2.—Average of blood levels and urinary excretions of gantrisin® in 2 patients after one 2 Gm. oral dose.

TABLE 2.—*Simultaneous Levels of Gantrisin® in Spinal Fluid and Blood of Patients Receiving 6 Gm. Daily*

	Spinal Fluid		Blood	
Patient	Free Form, Mg./100 Cc.	Total, Mg./100 Cc.	Free Form, Mg./100 Cc.	Total, Mg./100 Cc.
L. G.	2.8	2.7	6.7	8.2
I. K.	4.5	5.5	23.4	31.0
J. M.	2.4	2.9	11.5	15.3
	0.9	1.5	5.1	7.7
F. McG.	8.7	12.5	12.4	17.9
M. McG.	9.4	12.6	17.2	22.0
Averages	4.7	6.3	12.7	17.0

The levels of gantrisin® in the spinal fluid were found to be about one-third those in simultaneously drawn blood samples, as is shown in table 2.

To follow more closely the absorption and excretion of gantrisin,* patients were given a single 2 Gm. dose by various routes. Frequent blood samples were drawn for the determination of blood levels, and

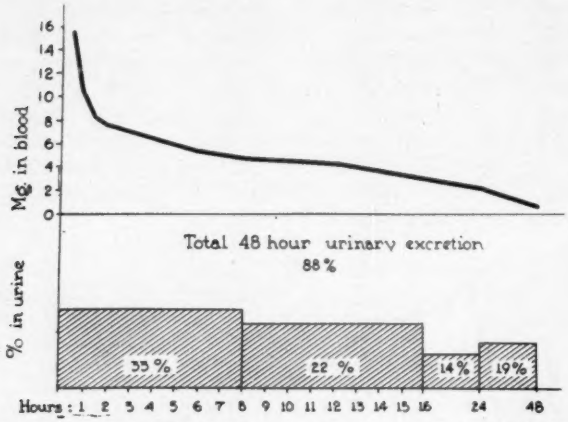

Chart 3.—Average of blood levels and urinary excretions of gantrisin* in 2 patients after one 2 Gm. intravenous dose.

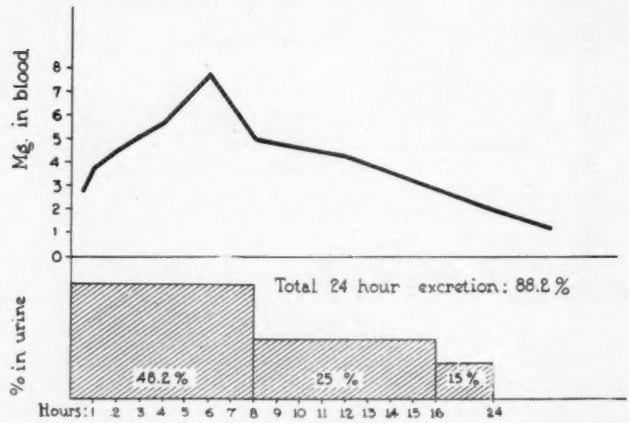

Chart 4.—Average of blood levels and urinary excretions of gantrisin* in 2 patients after one 2 Gm. intramuscular dose.

the sulfonamide excreted during a forty-eight hour period was measured. The results are shown in charts 2, 3 and 4.

The highest blood levels, 16 mg. per hundred cubic centimeters in thirty minutes, were obtained when the drug was given intravenously.

The concentration in the blood rapidly decreased, and 8 mg. per hundred cubic centimeters was left two hours after injection. The total forty-eight hour urinary excretion was 88 per cent of the original dose, 33 per cent being excreted during the first eight hours. When the drug was administered intramuscularly, a peak blood level of 8 mg. per hundred cubic centimeters was reached at six hours and 88.2 per cent of the administered dose was excreted in the urine in twenty-four hours. Blood levels of 9 mg. per hundred cubic centimeters were reached two to three hours after the oral administration of a single 2 Gm. dose, 94.3 per cent of the dose being excreted in forty-eight hours. The most rapid excretion occurred during the first eight hours.

It is appreciated that there is considerable variation in the rate of absorption among various persons when the drug is given orally or intramuscularly. The foregoing data give an idea of the rate of absorption in a limited number of patients of approximately average renal function and age.

The studies on excretion indicated that there is no appreciable retention of the drug provided the renal function is adequate. About 70 per cent of the excreted drug is in the free form, and the other 30 per cent is in the conjugated form.

COMMENT

There are still many places in the physician's armamentarium for sulfonamides. Renal complications have been the most serious danger; therefore, a more soluble sulfonamide should be of value. Our data and other mentioned reports on the use of gantrisin® indicate that it is a relatively safe compound, although the usual precautions required in sulfonamide therapy must be taken. Of these, an adequate fluid intake, usually 2,000 cc. or more for twenty-four hours, is the most important.

SUMMARY AND CONCLUSIONS

The use of gantrisin® in the treatment of 300 patients for a variety of conditions without the development of renal complications indicates that it may serve as a useful, relatively safe sulfonamide.

Studies on the solubility, absorption and excretion of gantrisin® suggest the following conclusions:

1. The solubility of gantrisin® rapidly increases between p_H 5.5 and 6.5, whereas a similar rise in the solubility of sulfadiazine occurs between 7.4 and 8.

2. Administration of 1 Gm. every four hours orally or intramuscularly or 2 Gm. every eight hours intravenously maintains adequate average blood levels. The highest levels are produced when the drug is given intravenously, the next highest when it is given intramuscularly and the lowest when it is given orally.

3. The intramuscular or intravenous administration of a 40 per cent solution of the ethanolamine or diethanolamine salts of the drug produces no reactions.

4. Eighty-eight to 90 per cent of the drug is excreted in the urine in the forty-eight hours after the administration of a single dose by any of the three routes, with the most rapid excretion occurring during the first eight hours.

5. Twenty-eight to thirty-five per cent of the drug appears in the urine in the conjugated form regardless of the mode of administration. A similar degree of acetylation occurs in the blood.

6. Levels of the drug in the spinal fluid are about one-third those in the blood.

WHIPPLE'S INTESTINAL LIPODYSTROPHY

Report of Four Cases and Discussion of Possible Pathogenic Factors

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AMONG debilitating diseases is a rare pathologic state of unknown cause first described in 1907 by Whipple.[1] It is characterized clinically by gastrointestinal distress with fatty diarrhea and failure of intestinal absorption leading to death. In some respects it resembles the sprue syndrome, but macrocytic anemia is lacking. In many of the cases there are chronic arthritis and hypotension. Postmortem examination reveals a striking and unusual picture of macrophages in the wall of the small intestine and fat granulomas of the mesenteric lymph nodes.

Four patients with this condition have come to autopsy in Duke Hospital: this we believe to be the largest series seen in any one clinic. One of these patients (case 1) was followed by one of us (J. P. H.) at intervals throughout his illness, and the diagnosis was made during life by means of biopsy of a mesenteric lymph node. We believe this to be the only confirmed case in which the diagnosis was made prior to autopsy. From a study of these cases and the literature there emerges a more precise definition of the disease and a concept of its pathogenesis.

REPORT OF CASES

CASE 1 [2]—*First Admission.*—A white business executive, aged 56, was admitted to Duke Hospital with symptoms of his final illness about one year before his death. He had been treated in the hospital three and a half years previously for weeping eczematoid dermatitis of the lower extremities. Large varicose veins were present in the legs. He weighed 190 pounds (86.2 Kg.) at that time. Routine laboratory tests and roentgenograms disclosed no significant abnormalities.

From the Departments of Medicine, Pathology and Biochemistry, Duke University School of Medicine.

1. Whipple, G. H.: A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues, Johns Hopkins Hosp. Bull. **18**:382-391, 1907.

2. This case report has been presented in some detail because, so far as we are aware, it represents the most complete account of the natural history of Whipple's disease.

He had suffered from severe malaria earlier in life, had experienced a "nervous breakdown" at age 47 with a blood pressure "as low as 80" and had had gonorrhea at age 18 without complications. For several years he had noticed "rheumatism" or pain in the right shoulder and elbow, without swelling of the joints. A chronic nonproductive cough had been present for years. His diet seemed to be adequate and well balanced. However, it was noted that he was particularly fond of highly seasoned foods and fatty portions of meat.

The patient came to the hospital on Nov. 19, 1943 because of weakness, loss of weight and increased severity of his cough. About two months previously he had contracted a cold, but he improved after a week of treatment with home remedies. However, at that time he accidentally inhaled chemical smoke from military maneuvers in his home town and this precipitated a paroxysm of coughing which lasted about an hour and left him exhausted and apprehensive. From that time he began to lose his appetite and to go downhill. There was little nausea but some uneasy discomfort in the abdomen, and he soon lost all desire for food. He also began to have diarrhea with several watery stools each day, which he attributed to medication of iron, and the stools were solid for a week after he stopped taking iron. However, diarrhea recurred intermittently throughout his illness, and the effect of iron is uncertain. There had been a little blood on the stool on one occasion, attributed to hemorrhoids. The cough had continued, and there was a little mucoid expectoration which seemed to come from the throat and nose. Some of the teeth were known to be in bad condition. His physician recently had found the blood count and blood pressure to be low. His weight had declined from 202 to 176 pounds (91.6 to 79.8 Kg.) in about six or seven weeks. There had been no fever.

Physical examination revealed a well developed white man who appeared weak and chronically ill. His height was 5 feet 9 inches (175 cm.), weight 172 pounds (78 Kg.) and blood pressure 100 systolic and 60 diastolic. He was somewhat short of breath on exertion, and there were occasional paroxysms of unproductive brassy cough. [It is of interest to note that Whipple's patient had this symptom and that it also was observed in our cases 2 and 3.] The ear drums were dull, and the right drum membrane was retracted. There were considerable dental caries, and the tongue was slightly red. The tonsils were small. Shotty lymph nodes were present in the inguinal regions, but no others were found. There was moderate emphysema, and a few coarse rales were heard at the base of the right lung posteriorly. The heart was not enlarged and abnormalities were not detected. There was some gaseous distention of the abdomen. By rectal examination there was slight tenderness, probably due to internal hemorrhoids, which were the only abnormality seen by proctoscopic examination. The prostate gland was within normal limits. Large varicose veins and pigmentation of the skin of the lower legs were noted. Results of neurologic tests were not unusual except that the patient was very sensitive to plantar stimulation and the Babinski reflex could not be evaluated.

The hemoglobin content was 9.5 Gm. per hundred cubic centimeters (61 per cent); red blood cells, 3,080,000, and white blood cells, 11,300, with neutrophilic polymorphonuclear 73 per cent, eosinophils 12 per cent, monocytes 4 per cent, large lymphocytes 5 per cent and small lymphocytes 6 per cent. A repeat blood count four days later showed essentially the same picture, with 13 per cent eosinophils. Results of urinalysis were normal. Serologic tests for syphilis gave negative reactions. Stools were brown and soft and gave strongly positive benzidine reactions for occult blood on two occasions. No ova or parasites could be found.

Fluoroscopic examination and a roentgenogram of the chest showed some diffuse bronchovascular thickening but no localized lesions. The heart was not enlarged, but the aorta was tortuous. A plain survey roentgenogram of the abdomen and roentgenograms of the sinuses showed nothing abnormal. Studies of the gastrointestinal tract at intervals after a barium sulfate meal revealed marked disturbance in the pattern of the entire small intestine. The colon appeared normal.

Otorhinolaryngologic consultation yielded the opinion that there was mild chronic tonsillitis and that the postnasal discharge was due to septal deviation. A very active gag reflex was noted.

The patient remained in the hospital seven days, during which time he ate moderately well of a soft diet, was afebrile, had no diarrhea and was reasonably comfortable. He did complain, however, of some epigastric fulness and burning, for which he received symptomatic treatment. The tentative diagnosis was placed among abdominal cancer, Hodgkin's disease, lymphosarcoma and intestinal tuberculosis. It was felt that the symptoms might be due simply to loss of appetite, poor diet and rapidly developing vitamin deficiency. The patient was eager to return home, and so he was given two transfusions of 500 cc. of citrated blood and discharged to the care of his local physician. He was advised to take whole liver extract by mouth and "crude" liver extract intramuscularly, ferrous sulfate, belladonna tincture and a bland diet. He was directed to return in a few weeks if not improved. Report by mail indicated little progress, and the patient returned about seven weeks after the last admission.

Second Admission.—At this time the chief complaint was diarrhea. The patient had been having one to seven loose or watery stools a day with some flecks of fresh blood at times. Loss of weight had continued, and he now weighed only 144 pounds (65.3 Kg.), representing an additional loss of 28 pounds (12.7 Kg.) in less than two months. His dyspepsia had continued, and he had begun to vomit rather frequently, bringing up food eaten several hours previously. He often took sodium bicarbonate for the digestive symptoms. The physical examination revealed no changes except for marked weight loss, lower blood pressure (90 systolic and 60 diastolic), increased redness of the tongue and some increase in pigmentation of the skin over the hands.

A blood count at this admission showed hemoglobin 7.8 Gm. per hundred cubic centimeters, red cells 2,470,000 and white cells 11,000 (polymorphonuclears 83 per cent, eosinophils 1 per cent, monocytes 1 per cent, large lymphocytes 4 per cent and small lymphocytes 11 per cent). The reticulocyte count was 5.2 per cent. The anemia remained approximately normochromic and normocytic in type. Stools at times were liquid, at other times light colored and pasty and occasionally hard and formed. They usually were rather foul. There was no gross blood in the stools, but the benzidine reaction for occult blood often was positive. While the patient was on a "soft diet," without specific limitation of fat, 59 per cent of the weight of the dried stool was fat.

Proctoscopic examination again showed small internal hemorrhoids but no bleeding. Roentgen studies after a barium sulfate enema showed nothing unusual. The lungs were clear roentgenologically. Roentgenograms of the teeth showed evidence of considerable infection. A plain roentgenogram of the abdomen showed normal conditions. The gallbladder failed to fill with iodoalphionic acid (priodax). Gastrointestinal examination after a barium sulfate meal at this time showed the stomach to be rather high, with some cascading. There appeared to be thickening of the mucosal folds in the duodenum and jejunum, and there was much segmentation and flocculation of the barium in the small bowel, with slight hypomotility (fig. 1).

A number of other laboratory tests were carried out during the almost seven weeks that the patient was in the hospital at this admission. A glucose tolerance test showed the following blood sugar levels: fasting, 85 mg. per hundred cubic centimeters; one-half hour after ingestion of glucose by mouth, 112 mg.; one hour, 109 mg., and three hours, 114 mg. There was no sugar in the urine. The Welt-

Fig. 1 (case 1).—Roentgenogram of the abdomen five hours after ingestion of a barium sulfate meal. Note the delay in emptying of the stomach, loss of continuity of the barium column in the small intestine and segmentation and flocculation of barium with loss of mucosal detail in the small bowel. This appearance is not specific for Whipple's disease but is common in conditions with disturbances of the physiology of the small intestine.

mann coagulation band was 8. Stool culture was negative for pathogens. The serum calcium level was 8.1 mg. per hundred cubic centimeters and the phosphorus level 3 mg. Determinations of serum lipase and urinary diastase were within

the normal range. In a sulfobromophthalein sodium excretion test of hepatic function a trace of dye was retained after forty-five minutes. The total plasma protein content was 6.5 Gm. per hundred cubic centimeters, of which 1.6 Gm. was albumin and 4.9 Gm. was globulin (albumin:globulin ratio 0.32). The nonprotein nitrogen level of the blood was 30 mg. per hundred cubic centimeters; the chloride level of the plasma, 544 mg.; the sodium level of the serum 143 and the potassium level 4.1 milliequivalents per liter (normal).

The patient's course was very variable, except in one respect: He continued to lose weight. In spite of all manner of supportive measures he left the hospital after seven weeks weighing 13 pounds (5.9 Kg.) less than on admission. There were repeated flare-ups of diarrhea lasting two to three days, with three to seven bulky, loose stools per day. At times there was a tendency toward constipation, and at other times the bowel movements were practically normal. The patient was tense and worried and continued to complain of "heartburn." The temperature averaged 36 to 37 C. (97 to 98.6 F.), and the pulse rate was 80 to 100 a minute.

Liver extract was administered in large doses, whole liver extract by mouth, and "crude" injectable extract intramuscularly. Later the latter was alternated with concentrated extract intramuscularly. Vitamin B complex tablets and vitamin A and D capsules also were given. The hemoglobin rose to 70 per cent and red blood cells to 3,460,000 in seventeen days. For a time the patient ate somewhat better of a bland low fat diet, but he continued to lose weight. Five transfusions, totaling 2,300 cc., of citrated blood then were given, with two minor chills. The blood count reached 80 per cent hemoglobin and 4,040,000 red cells, and the patient felt a little stronger. However, it was recognized that a diagnosis had not been made, and exploratory laparotomy was advised. This was refused, and the patient was discharged (Feb. 29, 1944) on a program similar to that just described, plus 0.6 Gm. of pancreatin three times daily with meals.

It was felt that he did not have sprue because of the absence of a macrocytic anemia, the persistence of occult blood in the stools and the persistence of symptoms and loss of weight after treatment with liver. Some increase in pigmentation of the skin over the hands and the persistence of hypotension suggested Addison's disease. However, the values for sodium and potassium in the serum were normal. Pancreatic insufficiency, mesenteric tuberculosis or lymphoma and cancer of the gastrointestinal tract still were considered to be the best possibilities for diagnosis.

Third Admission.—While at home the patient continued to take liver with fair regularity and gained some strength for a time. However, the bouts of diarrhea continued, as did gradual loss of weight. After two months, weakness became severer, and he was readmitted. He reported a recurrence of diarrhea several days before and complained of occasional vomiting and much gaseous distention. He had fainted and fallen the day before admission. His weight was about 120 pounds (54.4 Kg.), or 11 pounds (5 Kg.) less than that on discharge nine weeks earlier. The blood pressure was 88 systolic and 60 diastolic. The nail beds were pale, and the tongue was decidedly red, with definite papillary atrophy. There was much borborygmus, and the abdomen was protuberant, but no masses or viscera could be felt. At this admission Whipple's intestinal lipodystrophy was added to the list of diagnostic possibilities.

The hemoglobin now was 8.2 Gm. per hundred cubic centimeters; erythrocytes, 3,540,000, and leukocytes 4,100, with 86 per cent segmented polymorphonuclears, 4 per cent stab forms, 3 per cent small lymphocytes and 7 per cent monocytes. Reticulocytes comprised about 1 per cent of the total. Sternal bone marrow, obtained by puncture and suction, showed evidence of a full bone marrow but with

slight arrest of both the erythroblastic and the myeloblastic tissue. Urnalysis showed nothing abnormal except for a few white blood cells in the sediment. Stool fat was 40 per cent soon after admission, but with restriction of fat intake and increase in the dosage of pancreatin to 2.5 to 3.0 Gm. with each meal, it declined to 29 per cent (within normal range). The benzidine reaction for occult blood varied from a trace to three plus. A repeat glucose tolerance test (oral) gave the following blood sugar values: fasting, 77 mg. per hundred cubic centimeters; one-half hour after ingestion of glucose, 93 mg.; one hour, 100 mg.; two hours, 96 mg., and three hours, 90 mg. Results of the sulfobromophthalein sodium test of hepatic function and determinations of serum lipase and urinary diastase were essentially the same as during the preceding admission. The cephalin flocculation reaction was 3 plus. Bence Jones protein was found in the urine. The total serum proteins were 6.4 Gm. per hundred cubic centimeters, with an albumin : globulin ratio of 0.52. The blood calcium level was 8.1 mg. and the phosphorus level 2.8 mg. Plasma vitamin A was in the normal range, at 50 micrograms per hundred cubic centimeters, and carotene was very low, at 21 micrograms (average of two determinations). The heart and lungs again appeared normal on roentgen examination. The gallbladder now filled fairly well with iodoalphionic acid and contracted satisfactorily. The ribs and skull appeared normal on roentgenograms.

Because the possibility of pancreatic insufficiency had been considered as a diagnosis, studies were undertaken to learn whether or not pancreatic enzymes were present in the duodenum. With much difficulty, because of the hyperactive gag reflex, a tube was passed into the stomach and then into the duodenum. Fasting gastric contents contained 17 degrees of free hydrochloric acid and 32 degrees of total acid. Three specimens of duodenal contents were obtained, one before and two after the hypodermic injection of 10 mg. of methacholine chloride (mecholyl,* acetyl-beta-methylcholine chloride). The first sample was slightly acid to litmus but contained lipase, diastase and trypsin. The two samples obtained fifteen and thirty minutes after injection of mecholyl were alkaline and contained larger quantities of the enzymes. Hence it was concluded that the diarrhea was not due to pancreatic insufficiency, and administration of pancreatin was discontinued. Culture of the duodenal contents produced no growth, and microscopic examination revealed only a few blood cells, epithelial cells and cocci.

In preparation for operation, the patient received liver, vitamins, dextrose solution, 3,500 cc. of citrated blood in seven transfusions, 60 Gm. of protein hydrolysate per day by mouth and iron. He ate well much of the time of a bland low fat diet and actually gained about 5 pounds (2.3 Kg.) in weight during the first two weeks, even before transfusions were given. However, with recurrence of diarrhea the weight again dropped about to the level at admission. Hemoglobin rose to about 90 per cent and red cells to 4,500,000 after the transfusions. He complained frequently of stiffness and arthritic pain in the left shoulder.

Exploratory laparotomy then was carried out (June 20) with nitrous oxide-ether anesthesia. There was a general appearance of poor nutrition of the abdominal viscera. The liver, spleen, stomach, pancreas, intestines and kidneys seemed to be grossly normal. However, there was marked lymphadenopathy in the mesentery of the small intestines. Two nodes were removed, one for culture (which showed no growth) and the other for microscopic examination. The latter revealed "chronic lymphadenitis with giant cell reaction to substances, probably fatty." Further study of the sections and comparison with material from an autopsied case (case 2) led to the diagnosis of Whipple's disease.

The patient recovered very well. Six additional transfusions were given, and protein hydrolysate was administered intravenously until a severe reaction occurred. Diarrhea, distention and dyspepsia continued at intervals. The weight a few days before discharge, about nine weeks after admission, was 110 pounds (49.9 Kg.), 10 pounds (4.5 Kg.) less than at admission, or a loss of 92 pounds (41.7 Kg.) since the onset of illness. He was advised to continue the same program at home and also was given neostigmine bromide (prostigmin bromide®), 15 mg. after each meal, for a time, in the hope of increasing intestinal absorption. There was no indication of benefit.

After the diagnosis had been clarified, the patient was given bile salts by his family physician, because of the report of Pearse (table 1) of the control by bile salts of 1 case of what he believed to be intestinal lipodystrophy. He was given ox bile extract U. S. P. (glycotauro, Hinson, Wescott and Dunning), 0.6 Gm., six times daily for three to four weeks. Within a few days there was considerable improvement in appetite and digestion, with a gain of three to four pounds (1.3 to 1.8 Kg.) in three weeks. Sodium taurocholate (Merck) as used by Pearse then was given, 0.5 Gm. four times daily. Soon there was another episode of diarrhea, distention and anorexia. This subsided after a few days, but the improvement was not resumed. The sodium taurocholate then was replaced by the glycotauro but with little or no benefit, and episodes of diarrhea continued in spite of the therapy. In view of the intermittent nature of the patient's symptoms throughout his illness, it is uncertain how much of the temporary benefit resulted from the administration of bile salts.

Fourth Admission.—The patient remained at home for about fourteen weeks. He was readmitted in extremely emaciated and debilitated condition, obviously having lost considerable additional weight. He was not weighed because of the discomfort and difficulty involved, but his weight was estimated to be about 90 to 100 pounds (40.8 to 45.4 Kg.), or less than half of the body weight at the beginning of the illness. Diarrhea had been intermittent. Observations on physical examination were unchanged except for further weight loss, slightly lower blood pressure (about 80 systolic and 60 diastolic), an abscess in the buttocks at the site of injection of liver, beginning decubitus ulcer over the sacrum and edema of the lower legs.

The hemoglobin content was 6.5 Gm. per hundred cubic centimeters (41 per cent); red blood cells, 2,360,000, and white blood cells, 7,650, with 80 per cent polymorphonuclears, 1 per cent basophils, 4 per cent monocytes and 15 per cent small lymphocytes. A benzidine test for occult blood in the stool elicited a strongly positive reaction. The total serum protein level was 4.4 Gm. per hundred cubic centimeters (albumin 1.1 Gm., globulin 3.3 Gm. and the albumin:globulin ratio 0.33). The serum chloride level was 540 mg. per hundred cubic centimeters; calcium level, 6.5 mg.; phosphorus level, 2.7, and cholesterol level, 44 mg. The phosphatase activity was 5.7 Bodansky units. Plasma vitamin A and carotene were rather low, at 24 and 21 micrograms per hundred cubic centimeters, respectively. The fasting blood sugar level was 65 mg. per hundred cubic centimeters. Bence Jones protein was present in the urine.

The patient was very uncomfortable because of his extreme debility. Diarrhea and cramping pain in the lower abdominal region were more troublesome. The stools were light in color, liquid or soft, voluminous and foul. Camphorated opium tincture U. S. P. (paregoric) and codeine were required frequently. Seven additional transfusions of 500 cc. each were given. For several days the patient ate fairly well, but with exacerbation of symptoms he lost all appetite and refused most

oral medication. There was little subcutaneous tissue in which to inject medicaments. After some temporary symptomatic improvement, the downhill course was resumed, the edema increased and there was further fall in blood pressure. Adrenal cortex extract, 4 cc. a day, then was given but produced no change. The patient lost strength rapidly during the last few days and died eighteen days after admission and about one year after onset of symptoms. The temperature was not above normal and usually remained subnormal.

Autopsy.—The body was that of a middle-aged, well developed, emaciated white man. The skin of both feet was edematous and pitted on pressure. Areas of brown pigmentation measuring up to 10 by 15 cm. were present in the skin of the medial ankle areas. There were moderate hypertrophic arthritic changes of the fingers, and both knees appeared enlarged and knoblike.

Within the peritoneal cavity was approximately 400 cc. of clear straw-colored fluid. The omentum was adherent to the abdominal wall by fibrous adhesions, particularly in the line of a healed laparotomy incision.

Approximately 400 cc. of an amber-colored, somewhat cloudy fluid was present in the left pleural cavity; the right pleural cavity contained 150 cc. of similar fluid. The pericardial cavity was not remarkable. There were no adhesions or other evidence of old or recent pericarditis. The heart weighed 310 Gm. An irregular dark brown softened area 2.5 cm. in longest diameter was present at the base of the posterior wall of the left ventricle. The remainder of the myocardium was not remarkable. On the closing margin of the right mitral cusp was a firmly attached white, hard, nodular mass 7 mm. in diameter. In a similar position on the left mitral valve was a smaller mass, 3 by 6 mm., of somewhat softer consistency. Several smaller nodules showing brown discoloration were scattered along the closing margin. The chordae tendineae were not thickened or fused. The remaining valves, the coronary ostia and arteries and the aorta presented no lesions.

The upper lobe of the right lung was completely consolidated. It was firm and on section showed a prominent granular, dry surface. The upper portion of the lower lobe of this lung was occupied by a typical area of hemorrhagic infarction. Its center was gray and softened. The entire upper lobe of the left lung was consolidated, as was a large part of the corresponding lower lobe. The lymph nodes at the hilus showed only anthracosis.

Aside from marked congestion, the liver, which weighed 1,330 Gm., did not appear remarkable. The gallbladder showed no lesions; no stones were present, and the extrahepatic bile ducts were patent throughout. The pancreas weighed 70 Gm.; externally and on section it presented no remarkable changes; its ducts were patent. The spleen was somewhat increased in size and weighed 170 Gm. The pulp was deep red and soft, and trabeculae were not prominent. The renal capsules stripped with difficulty, revealing finely granular surfaces. The upper pole of the right kidney was converted into a large smooth-walled cyst surrounded by a fibrous capsule. The ureters were patent. The adrenal glands were not remarkable except for the complete absence of the usual yellow cortical pigment.

The intestines were filled with a moderate amount of brown-black semisolid feces. The mucosa of the terminal portion of the jejunum and the greater portion of the ileum was marked by the presence of minute gray granular projections (fig. 2*A*), which lent the coat a velvety appearance. The areas in the ileum corresponding to Peyer's patches were prominent and showed the same change. There were two diverticula in the large bowel. No inflammatory phenomena were present. The mesentery contained a large amount of fat. Embedded in the adipose tissue were numerous lymph nodes (fig. 3*A*), which varied in size from a few

millimeters to about 4 cm. in greatest dimension. The larger ones were marked by complete absence of normal lymph node structure. They were pale except for cortical zones of hemorrhage, which in some instances were found within the center of the nodes. They contained numerous minute cysts, some of which were filled with yellow to white material suggestive of fat. There was no indication of blocked lymphatics, and the region where the thoracic duct is usually found was not remarkable. The periaortic and iliac lymph nodes showed changes identical to those just described.

The sternal, rib and femoral bone marrow did not appear abnormal.

Microscopic Examination.—The myocardium in the region described grossly as soft and brown consisted of numerous small infarcts. Some were old, consisting of hyalinized fibrous tissue; others were more recent, containing numerous fibroblasts and vessels, many of them capillaries, and infiltrated by inflammatory cells, among which macrophages predominated. Nowhere could obstruction of vessels be seen. The coronary arteries, however, did show moderate thickening

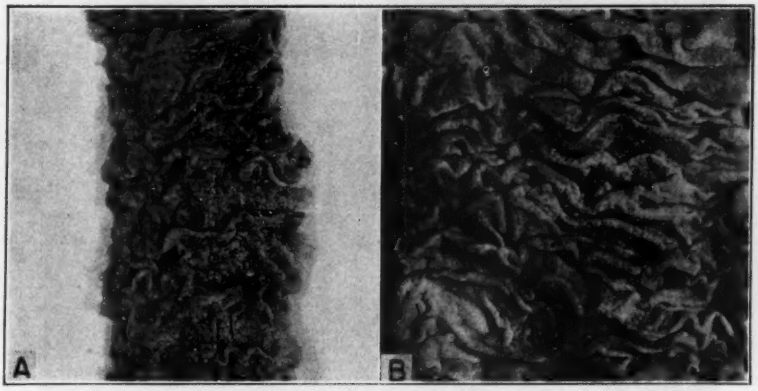

Fig. 2.—*A*, (case 1), ileum with prominent macrophage-laden villi; *B* (case 3), jejunum showing thickened mucosal folds and prominent macrophage-laden villi.

of their walls, largely due to intimal fibrosis. The epicardium was infiltrated over the areas of healing ischemic necrosis by the same type of inflammatory cells as have just been described. The surface of the epicardium was composed of a thin layer of hyalinized connective tissue. The nodules described on the mitral valve consisted of fibrous tissue containing collections of pseudoxanthoma cells which lay within the thickened valve. In these regions there was evidence of old and fresh hemorrhage. The entire zone was surrounded by a round cell exudate which could be followed to the base of the valve. In one area corresponding to the largest nodule described in the right leaflet the surface was ulcerated and covered by a thin membrane of fibrin.

Study of the left upper pulmonary lobe revealed diffuse consolidation. The pleura was lined by a fibrinopurulent exudate. The area described as an infarct showed marked hemorrhage into the alveolar spaces and destruction of the alveolar walls. No vascular obstruction was demonstrable. The upper lobe of the right lung was completely consolidated.

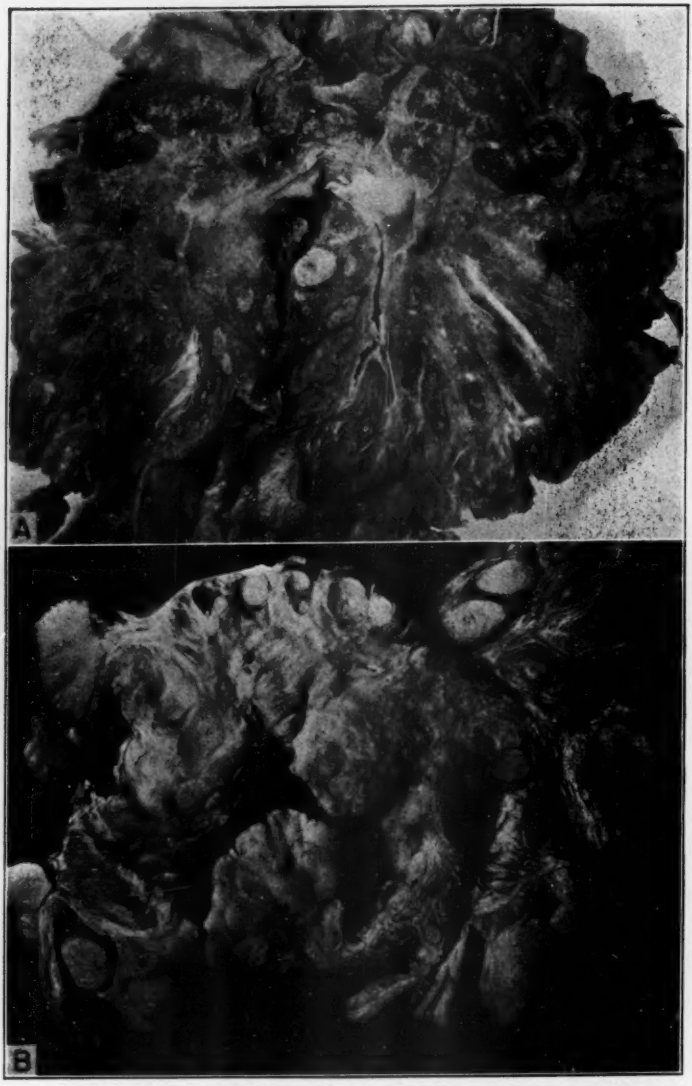

Fig. 3.—*A* (case 1), mesentery and microcystic, partly hemorrhagic lymph nodes; *B* (case 3), mesentery and enlarged microcystic lymph nodes.

The spleen contained numerous reticuloendothelial cells, many of which showed the presence of iron-containing pigment. Numerous plasma cells were scattered about the organ. The follicles were not prominent, and there were no germinal centers.

The pancreas showed characteristic structure; however, many of the acini were disrupted. The interstices were sparsely but diffusely infiltrated by round cells, among which were numerous monocytes.

In the periadrenal fat tissue there were numerous round cells and occasional polymorphonuclear leukocytes. The organ itself, however, was not remarkable.

Both kidneys were the site of characteristic arteriosclerosis and arteriolosclerosis. The subcapsular parenchyma was replaced in large part by fibrous tissue, within which obliterated hyalinized glomeruli were still visible. These zones were infiltrated by lymphocytes and plasma cells. The tubules were not remarkable except for their atrophic appearance in the region of fibrous replacement. The pelves were lined throughout by characteristic epithelium, and the submucosa showed a moderate degree of round cell exudate.

Sections through the ileum and the colon revealed an identical appearance. The ubiquitous round cells normally seen in the submucosa were replaced by vacuolated macrophages (figs. 4 *A* and 5 *A*), which, as stains for fat demonstrated, were not sudanophilic, except for an occasional cell containing a few particles of lipid. The sudanophilic material was isotropic. There were no dilated lymphatics to be seen. Round to oval spaces varying in size from the diameter of a narrow villus to that of three or four macrophages were scattered about. They showed no particular anatomic relationship to the central villous chyle duct and were not lined by endothelium. They contained sudanophilic material. The peritoneum of the large bowel was thickened by early fibrosis and infiltrated by numerous round cells. Numerous sections of the enlarged mesenteric lymph nodes revealed replacement of the follicular structure and pulp with macrophages, most of which were filled with lipid material which stained red with scarlet red. Groups and single nonsudanophilic macrophages identical with those in the intestinal mucosa were likewise present (fig. 5 *B*). Occasional zones in which plasma cells, lymphocytes and nonphagocytic monocytes were present could be seen. There appeared to be no increase in the fibrous tissue of the nodes. Large spaces, many of which were lined by multinucleated giant cells, were present (fig. 6 *A*). In these spaces, in frozen sections, fat and fatty acid crystal bundles could be demonstrated.

The diagnoses were intestinal lipodystrophy; endocardiosis of the mitral valve; diffuse pneumonia of the left lung and the upper lobes of the right lung; focal healing and healed areas of myocardial necrosis of the posterior wall of the left ventricle; chronic passive visceral congestion; ascites (400 cc.); hydrothorax (400 cc. left, 150 cc. right); pitting edema of the feet; hemorrhagic infarct of the right upper pulmonary lobe; mild chronic pancreatitis; renal arteriosclerosis and arteriolosclerosis; hypertrophic arthritis of the fingers and knees; cyst of the right kidney; diverticula (two) of the large bowel.

CASE 2.—A 52 year old white farmer was admitted to the hospital on three occasions. He first was seen in the outpatient clinic seven and one half years before death, when he gave a history of frequent infections of the respiratory tract and nonproductive cough. Paroxysms of coughing often would cause vomiting. The tentative diagnosis was chronic bronchitis, but the patient did not return for a roentgenogram of the chest. The hemoglobin was 11.9 Gm. per hundred cubic centimeters (77 per cent) and albumin (1 plus) and occasional red blood cells were found in the urine. The weight was 115 pounds (52.1 Kg.), the height 5 feet 7 inches (201 cm.).

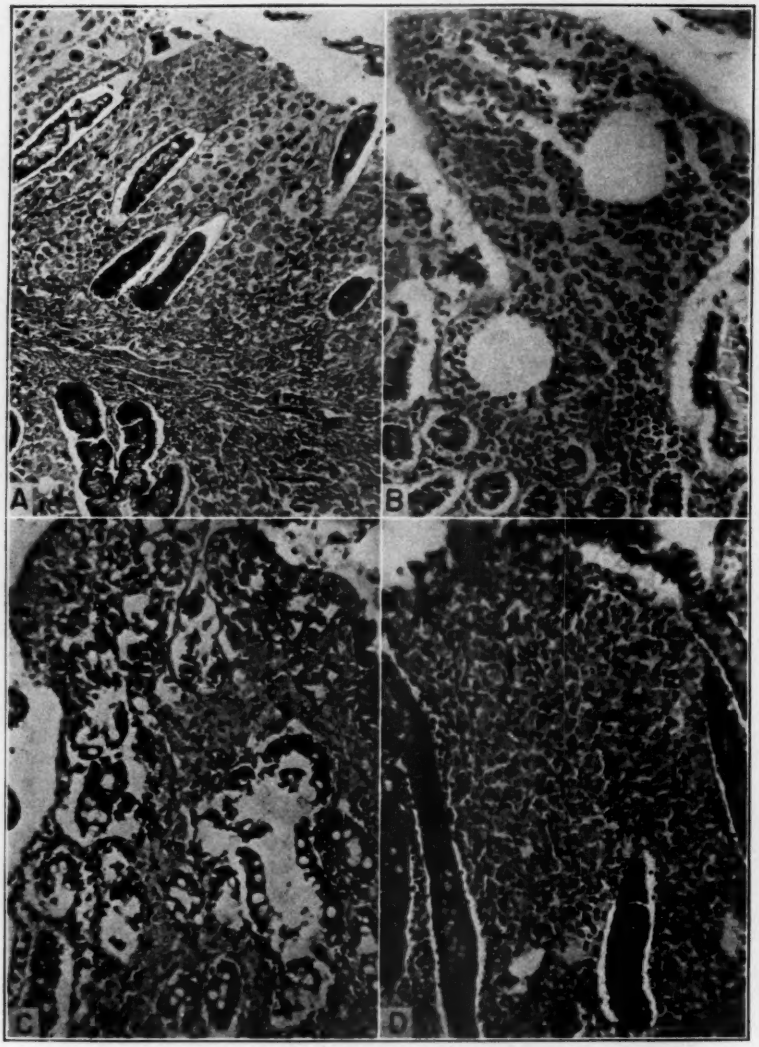

Fig. 4.—*A* (case 1), *B* (case 2), *C* (case 3) and *D* (case 4) all illustrate the characteristic mucosal macrophagocytosis. *B* reveals the round mucosal spaces formerly occupied by sudanophilic substance (fat).

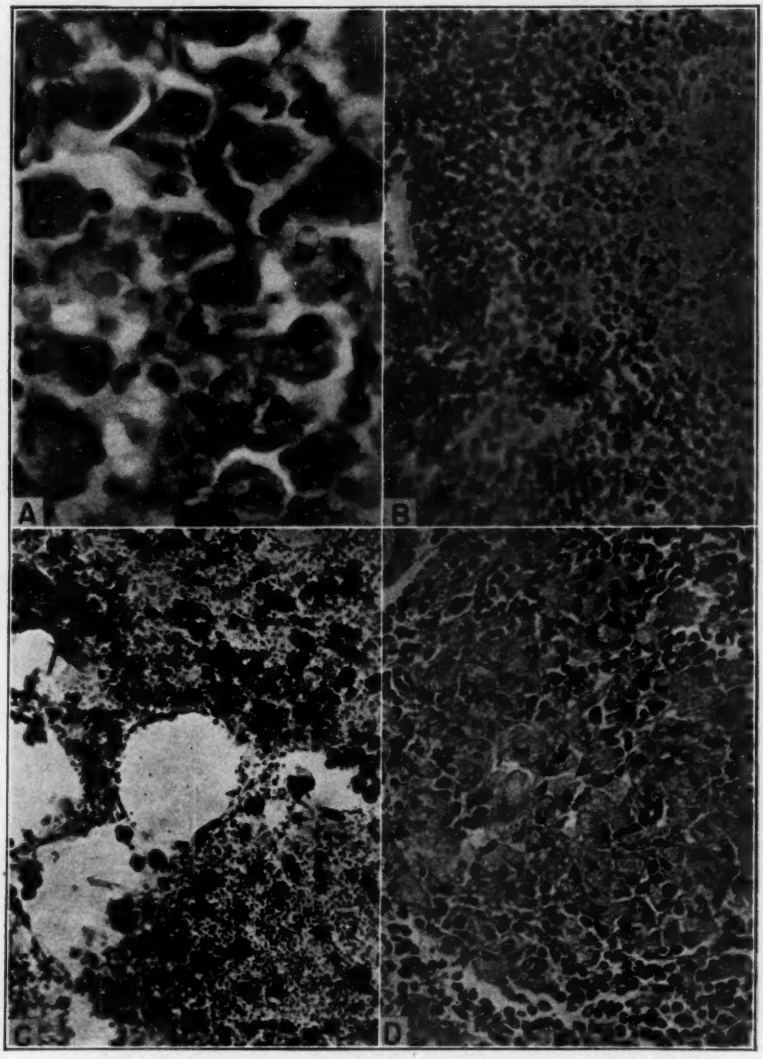

Fig. 5.—*A* (case 1), high power view of vacuolated intestinal mucosa macrophages. *B* (case 1), sudan IV–preparation of mesenteric lymph node showing a few macrophages filled with globules of sudanophilic (black) substance. The very pale cells are nonsudanophilic macrophages. *C* (case 3), sudan IV–stained mesenteric lymph node showing distribution of fats, in stromal macrophages and large spaces. The fat has largely fallen out of the spaces. *D* (case 4), focal collection of sudanophilic macrophages in spleen.

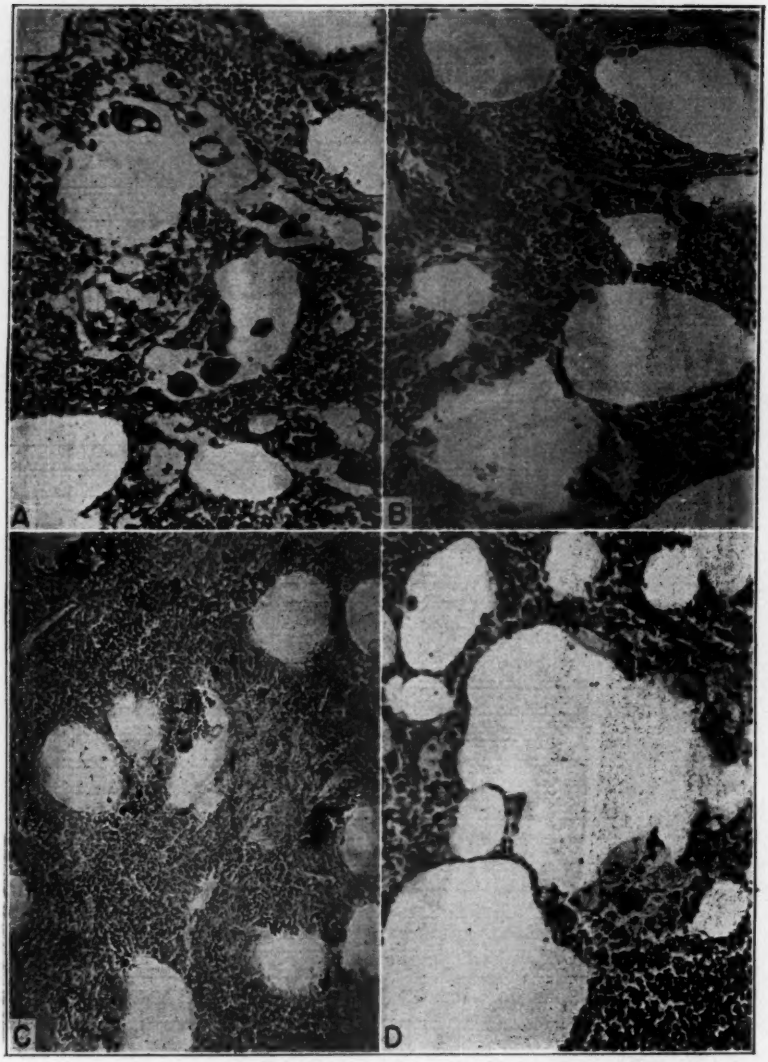

Fig. 6.—*A* (case 1), *B* (case 2), *C* (case 3) and *D* (case 4), lipogranulomatosis of the mesenteric lymph nodes. The large spaces are, in appropriately prepared sections, filled with fat and crystals. Many of these are cholesterol; others, presumably fatty acids. Lipid-containing macrophages and multinucleated giant cells line the spaces. Numerous groups and individual nonsudanophilic and sudanophilic macrophages are present in the stroma, as well as plasma cells, eosinophilic leukocytes and monocytes. *C* is a photomicrograph of the only lymph node extant from case 3 (sudan IV stain).

The patient was next seen about eight months before death, when he was admitted to the hospital because of symptoms related to his final illness. The family and marital histories were not significant except that his wife had had pellagra. He stated that his past health never had been very good but as a young man he had weighed 155 pounds (70.3 Kg.). He had suffered several attacks of "influenza" which became progressively severer. At age 42 he had pneumonia, "whooping cough" and malaria. He also had had typhoid, kidney colic and an appendectomy. There had been repeated attacks of hot, swollen and painful joints during adult life.

About three months before admission he began to have pain low in the abdomen, and this was followed by nervousness and weakness. He also had been troubled by headache and had taken many powders containing acetanilid and bromides. The pain gradually worked up to the upper part of the abdomen and seemed to be aggravated by food. He had vomited once after taking some medicine from his physician and had experienced one shaking chill. There had been some bright blood on the stool when he was constipated.

The weight was only 101 pounds (45.8 Kg.) and the blood pressure 122 systolic and 66 diastolic. Small epitrochlear nodes were felt. The teeth were carious and the tongue smooth. The lungs were clear, and the heart was not enlarged, but there were systolic and diastolic murmurs at the aortic area and a systolic murmur at the apex. The abdomen was tense, and there was tenderness in the lower quadrants.

The hemoglobin was 8.8 Gm. per hundred cubic centimeters (57 per cent); erythrocytes 3,190,000, and white blood cells, 7,600, with 81 per cent polymorphonuclears, 2 per cent eosinophils, 1 per cent monocytes, 3 per cent large lymphocytes and 13 per cent small lymphocytes. Serologic tests for syphilis elicited negative reactions. The blood nonprotein nitrogen level was 34 mg. per hundred cubic centimeters. A urine concentration test showed a maximum specific gravity of 1.022, and the phenolsulfonphthalein test indicated 60 per cent excretion of the dye in two hours. However, the urine contained a trace of albumin and rare casts. Examination of the stools was noncontributory. The erythrocyte sedimentation rate was 28 mm. per hour, corrected. The electrocardiogram was within normal limits. A roentgenogram of the chest showed the lungs clear and the heart normal in size. Examination of the gastrointestinal tract after a barium sulfate meal showed marked spasm of the duodenum, but no ulcer crater could be seen.

The patient had a low grade fever but improved on bland diet and symptomatic treatment. Exploratory laparotomy was advised because abdominal cancer was suspected. However, the patient rejected the advice, and he was discharged after eighteen days in the hospital. It was felt that he had chronic nephritis and rheumatic heart disease in addition to the undiagnosed abdominal condition.

He returned about six months later because of watery diarrhea of three weeks' duration. There had been no blood or mucus in the stools, but pain low in the abdominal region recurred with the diarrhea and the patient had lost weight and strength. Physical examination was unchanged except for progressive emaciation his weight being 93½ pounds (42.4 Kg.). There were some nausea and vomiting. The temperature remained normal, but there was additional weight loss of 5 pounds (2.3 Kg.) during two weeks in the hospital. However, the diarrhea subsided and the patient felt better after treatment with liver extract, transfusions and other supportive measures.

At this admission the blood count was about as before, except that 4 per cent eosinophils were found. Results of urinalysis also were the same. However, the stool showed a strongly positive reaction for occult blood and the nonprotein

nitrogen level of the blood had risen to 58 mg. per hundred cubic centimeters. A glucose tolerance test gave the following values: fasting blood sugar, 78 mg. per hundred cubic centimeters; one-half hour after ingestion of glucose 115; one hour, 126; two hours, 120, and three hours, 100. Proctoscopic examination disclosed no abnormalities, and roentgen study of the gastrointestinal tract after a barium sulfate meal and barium sulfate enema showed no lesions. Fat was 51 per cent of the dried weight of the stools.

It was felt that the patient might have sprue, and he was advised to continue liver therapy at home. However, soon after discharge his diarrhea and abdominal cramps recurred. He was readmitted after only five weeks at home, during which time his weight had declined to 80 pounds (36.3 Kg.). In addition to diarrhea, he complained of nausea, vomiting, loss of weight, hiccups and pain in the right shoulder and upper arm. His general condition was poor; there was a uriniferous odor on the breath, and the patient was drowsy. The blood pressure now was 76 systolic and 30 diastolic. The other findings were essentially as before. The blood count was similar to previous findings but the urine now gave a 2 plus reaction for albumin and contained many white blood cells. The nonprotein nitrogen had risen to 175 mg. per hundred cubic centimeters and the carbon dioxide–combining power of the plasma was 22 volumes per cent. The serum calcium was 4 mg. and the phosphorus 15 mg. per hundred cubic centimeters. Plasma proteins were 5.6 Gm. (albumin 2.4 Gm. and globulin 3.2 Gm.).

In spite of transfusions and supportive treatment, the patient went steadily downhill and died after only three days in the hospital. There was a terminal rise in temperature to 38.2 C. (100.8 F.).

Autopsy.—The patient was a well developed but extremely emaciated white man. The lower part of the abdomen and extremities showed marked pitting edema. The abdominal cavity was lined by smooth peritoneum and contained approximately 2,000 cc. of straw-colored fluid. A few firm fibrous adhesions bound the colon to the abdominal wall at the site of a well healed McBurney incision. In the left upper quadrant similar, but denser, fibrous adhesions were present. The pleural and pericardial cavities were not remarkable.

The heart weighed 400 Gm. Its epicardium was somewhat roughened. The aortic cusps were thickened and were the site of marked calcification, producing a rigid stenotic orifice. On the three cusps there were friable vegetations. The largest, on the posterior cusp, measured 2.5 mm. in diameter and projected into the lumen for about 3 mm. The surface of the aortic leaflet of the mitral valve was wrinkled and yellow. The remainder of the organ was not abnormal.

The right lung weighed 950 Gm. The lower lobe was consolidated. There appeared to be a few areas of pneumonia in the lower lobe of the left lung.

The spleen was not enlarged; it weighed 130 Gm. Its capsule was thickened by fibrosis, and the pulp on section was scraped away with some difficulty. The liver weighed 1,500 Gm.; its capsule was wrinkled but glistening. On section, the normal architectural structure was accentuated, and the parenchyma possessed a yellow tinge. The gallbladder and bile ducts were normal.

The pancreas weighed 70 Gm. and appeared normal. The renal capsules stripped with ease, revealing pale surfaces and congested stellate veins. After sectioning, the cortices appeared to be decreased in thickness, approximately one-third the expected width. Small brownish foci, suggestive of old hemorrhages, were present in this zone. The usual striated appearance of the renal surface was partially obliterated. The pelvic mucosa was marked by a few small hemorrhages The adrenal glands were normal in appearance.

The jejunum and ileum were somewhat thickened, and the mucosa was gray and fuzzy.

Microscopic Examination.—The myocardial fibers and the valves were normal except for the aortic cusp of the mitral valve. This was thickened by hyalinized fibrous tissue, containing calcium salts near its surface. At the base of a cusp were groups of dilated capillaries, small arteries and veins. Among these were scattered macrophages containing old blood pigment. Lining the surface, facing the lumen, the connective tissue appeared to have undergone fibrinoid change and contained large, distorted fibroblasts. There were no bacteria visible.

In the right lung were small foci of pneumonia. The bronchioles were surrounded by round cells, but their epithelium was intact.

The architecture of the liver was essentially normal. The central venules and the sinusoids were congested, and there were occasional foci in which the central portion of the liver cords had undergone atrophy. In several such areas there was evidence of an acute reaction represented by a few polymorphonuclear leukocytes. The portal fields and their structures were not remarkable.

The interstices of the kidneys were diffusely infiltrated by round cells. Occasional tubules, particularly in the convoluted portion, were filled with polymorphonuclear leukocytes. The glomeruli were not remarkable except for a varying degree of fibrosis, accentuated in some areas and resulting in characteristic hyalinized bodies.

The parenchyma of the pancreas was essentially normal. The ducts, acini and islets appeared unchanged. However, the interstices of the organ were sparsely infiltrated by leukocytes, among which small monocytes and lymphocytes predominated.

In the spleen were numerous collections of macrophages loaded with blood pigment. There were a scattering of polymorphonuclear leukocytes and moderate congestion of the sinusoids. The lymphoid follicles were small and possessed poorly developed germinal centers. The fibrous capsule showed some thickening.

The stomach and colon were not remarkable. No evidence of lymphatic obstruction was visible; however, sections of jejunum and ileum revealed large pale macrophages distending the villi and replacing the usual round cells of the mucosa (fig. 4*B*). The macrophages contained globules of material whose nature has not been determined. Tissue suitable for fat stains was no longer available. In some areas there were large and small round spaces which were probably occupied by fat. In the duodenum Brunner's glands were surrounded by fibrous tissue, among which were some round cells diffusely infiltrating the submucosa and the subserosa.

The mesenteric lymph nodes had lost their normal appearance (fig. 6*B*). In hematoxylin and eosin preparations no follicles were discernible. The nodes were, however, characterized by the presence of large and small round spaces lined by foamy macrophages and giant cells of the characteristic foreign body type. Scarlet red stain revealed the presence in these spaces and in the macrophages of fat and bundles of fatty acid crystals. The fibrous stroma contained numerous lymphocytes, monocytes, foamy macrophages (fat containing), occasional plasma cells and eosinophilic leukocytes.

The diagnoses were chronic pyelonephritis (uremia); intestinal lipodystrophy; cachexia; aortic endocardiosis; calcific aortic stenosis; ascites; pitting edema of lower part of abdomen and extremities; diffuse focal pneumonia of lower lobes; chronic passive visceral congestion; early focal centrolobular hepatic necrosis; perisplenic fibrosis; diffuse mild chronic pancreatitis.

CASE 3.—A white man aged 45, a nightwatchman, was first seen in this hospital about four years before his death (Oct. 14, 1940). At that time he was examined in the orthopedic clinic because his chief complaint was pain in the lower part of the back. It also was mentioned that for the preceding nine months he had experienced intermittent soreness in the shoulders, elbows, knees and ankles, one or two joints being involved at the time. However, he had not noted swelling of the joints. His appetite was reported as good, and his bowel habits were regular. No specific mention was made of digestive symptoms, but it was stated that the patient frequently took soda after eating. He also mentioned having mild sore throat most of the time and said that his mouth often felt "sore and rough."

The patient reported his weight as 151 pounds (70.3 Kg.), saying that he had lost 25 pounds (11.3 Kg.) in the past year. Unfortunately, he was not weighed in the clinic. Examination showed stiffness and limitation of motion of the lumbar portion of the spine, some nasal obstruction on the right, dental caries and large hyperemic tonsils. The chest was barrel shaped, but the lungs were clear. The heart appeared to be normal, and the blood pressure was 122 systolic and 78 diastolic. A rectal stricture was present. Roentgenograms of the lumbosacral portion of the spine showed advanced hypertrophic changes. The Wassermann reaction of the blood was negative.

The patient reported considerable improvement of the pain in his back five months later after wearing a brace and limiting his activities. He then was not seen again until he was admitted to the medical ward, desperately ill, four days before death.

Little is known about his condition in the interim because the patient was so ill when admitted that he could not give an adequate history and the family did not know details of his illness. The family and marital histories were not contributory. In the past history there was mention of pellagra at age 20 with scaling erythema of the arms. He had "double pneumonia" at about the same age. Malaria seven to eight years and arthritis four to five years before admission were mentioned. Review of systems revealed a history of intermittent headache of moderate severity in the left temporal region for one year, some impairment of vision for about a year, frequent colds and postnasal drip, chronic cough productive of mucoid sputum, occasionally blood streaked, with colds in the chest. Occasional smoky or cloudy urine also had been noted.

Several years before admission he became constipated and required frequent laxatives. There also was some "heartburn" attributed by the patient to chewing tobacco. Approximately one year before admission he lost his appetite and began to have burning discomfort and the sensation of gas in the upper part of the abdomen after meals. Nine months before admission he began to vomit, and this continued for several months, after almost every meal. There was no blood in the vomitus, only food recently eaten. The vomiting gradually diminished and ceased entirely about four and one-half months before he came to the hospital. Several weeks before vomiting stopped, he began to have diarrhea, beginning with three or four stools a day, but after one month there were as many as eighteen to twenty a day. Diarrhea persisted throughout the remainder of his illness. The stools were described as watery, frothy and foul smelling and were said to contain recognizable food particles as soon as thirty minutes after the food was eaten. There was some cramping lower abdominal pain with the diarrhea. No blood had been seen, and the stools had been dark only while iron was being taken. There had been a loss of about 75 pounds (34 Kg.) in weight, and weakness was progressive. Liver extract had been administered without improvement. There had been repeated roentgen examinations of the gastrointestinal tract, which the family thought had shown only rapid progression of the barium through the bowel.

The temperature, pulse and respiration were normal. The blood pressure was 95 systolic and 62 diastolic. The patient was very emaciated and weak but in no acute distress. He weighed about 86 pounds (39 Kg.). The skin was dry, loose and inelastic. There was no lymphadenopathy. The left maxillary sinus was cloudy on transillumination. There was some cheilosis, and the tongue was red, with papillary atrophy. The tonsils were small. The lungs were clear, and no murmurs were heard over the heart. The abdomen was slightly distended, and hypermotility of the bowel was evident. There was no tenderness, and no masses or organs could be felt, except the bowel. The prostate gland was slightly enlarged.

The hemoglobin was 10.2 Gm. per hundred cubic centimeters (66 per cent); red blood cells, 4,000,000, and white blood cells 11,280, with segmented polymorphonuclears 79 per cent, small lymphocytes 18 per cent, eosinophils 1 per cent and monocytes 2 per cent. The sedimentation rate was 26 mm. per hour corrected. The clotting time was four minutes, and the bleeding time two minutes. Platelets numbered 175,000. The prothrombin time was twenty-five seconds and the control twenty seconds.

Serologic reactions for syphilis were negative. The urinary sediment contained 10 to 15 white blood cells per high power field. Gastric analysis showed no free hydrochloric acid before or after hypodermic injection of histamine; the total acid was 1 degree after injection of histamine. The only stool specimen examined was thick liquid with a "tomato juice" appearance. The patient had received tomato juice as part of a liquid diet. There was no evidence of blood, and staining for fat was negative. However, the patient was not receiving fat in his diet. The blood sugar was 81 mg. per hundred cubic centimeters. The plasma vitamin A content was 23 micrograms and the carotene 10 micrograms (very low). A roentgenogram of the chest on the day of admission showed no changes in the lungs. A survey roentgenogram of the abdomen showed no abnormalities except gas in the small intestine. Fluoroscopic study after a barium sulfate enema revealed a sluggish colon, but no intrinsic lesions were seen. Further roentgen studies were not undertaken because of the patient's critical condition.

The patient's course went downhill steadily, in spite of intravenous administration of fluids and vitamins. Stools averaged four or five a day. On the third day signs of bronchopneumonia developed, with a leukocyte count of 35,000, and sulfadiazine was administered. The pulse rate rose rapidly, and digitalis was given. The temperature, which had been little above normal, rose abruptly to 38.5 C. (101.4 F.) on the fourth day, and the patient died.

Autopsy.—The patient was an emaciated white man. The peritoneal and pleural cavities contained no excessive amounts of fluid. Thin focal fibrous pleural adhesions were present bilaterally, and extensive fibrous adhesions bound the pericardium to the epicardium. Both cardiac ventricles were dilated although not hypertrophied. The aortic and pulmonary cusps were not unusual. The mitral valve, however, was the seat of several fibrous plaques. A number of rather friable vegetations were present near the line of closure of the tricuspid valve. The largest measured 0.5 cm. in diameter. When removed, they revealed a yellow discoloration of the underlying tissue. Terminal branches of the chordae tendineae were fused. However, the scarring was only minimal. The myocardium, coronary ostia, coronary arteries and aorta were normal in all respects. The bases of both lungs were consolidated. They were firm and voluminous and on section showed the variegated appearance of focal pneumonia.

The liver weighed 1,500 Gm. The capsule was tense but smooth and glistening throughout. On section the parenchyma showed the yellow discoloration of fat replacement. The architecture of the organ was essentially normal. About the

hilus there were a few elongated lymph nodes which measured up to 2 cm. in greatest dimension. On section they presented a homogeneous pale yellow surface. One showed the presence of numerous small cysts, not more than 1 mm. in diameter. These lymph nodes were similar to those to be described in the mesentery. The wall of the gallbladder was thickened by serosal fibrosis. The mucosa, however, was velvety and bile stained. No calculi were present, and the extrahepatic bile ducts were patent. The pancreas did not appear remarkable, and its duct was patent. The capsule of the spleen, which weighed 150 Gm., was marked by the presence of a few fibrous adhesions. The trabeculae and pulp were not abnormal.

The adrenal glands, the genitourinary system and the rectum were not unusual. The esophagus and stomach showed no abnormalities; however, the mucosa of the jejunum was finely granular and dull (fig. 2 *B*). The same appearance was seen in the ileum. Here, however, it was less striking. The wall of the gastroenteric tract was nowhere thickened or perforated, and the serosa was everywhere glistening and transparent. The mesentery was very fatty and contained numerous enlarged lymph nodes (fig. 3 *B*). Close to the base of the mesentery the nodes were largest. On section they all showed pale yellow-white surfaces marked by numerous minute cysts. The periaortic lymph nodes, particularly about the base of the celiac axis and the inferior mesenteric artery, were similar in all respects, except that they were the largest encountered, measuring up to 3 cm. in greatest dimension. There was no evidence of obstructed lymph vessels. Examination of the brain showed no lesions.

Microscopic Examination.—The epicardium was thickened by fibrosis and a subjacent zone of granulation tissue composed of fibroblasts, capillaries and inflammatory cells. The largest number were monocytes and lymphocytes. However, numerous polymorphonuclear neutrophils were likewise present. The myocardium was normal. The tricuspid valves showed vegetations consisting of homogeneous pink-staining material enclosing many spaces within which an occasional leukocyte was present. The surface adherent to the valve was the site of early organization. The leaflets were thickened by fibrosis and contained foci of hyaline degeneration and areas marked by numerous vacuolated macrophages.

Groups of alveoli of the lower pulmonary lobes were filled with neutrophil leukocytic exudate. Other groups were occupied by acellular pink granular material characteristic of edema fluid. A few of the pulmonary veins contained small nonoccluding mural thrombi.

The liver portal fields were not remarkable. The hepatic sinuses were moderately distended by blood, and there were focal areas of fat accumulation within the parenchymal cells in the peripheral zones of the liver lobules.

The pancreatic structure was not remarkable. The acini showed the usual appearance, and the ducts were patent. The splenic capsule was thickened by fibrosis and showed the presence of a few adhesions. The lymphoid follicles were not particularly well developed; however, the presence of large groups of macrophages filled with blood pigment stood in the foreground of every field. There appeared to be no increase in fibrotic tissue. The reticuloendothelial cells were hyperplastic, and there were numerous scattered neutrophilic and eosinophilic polymorphonuclear leukocytes. Associated with some of the trabeculae were groups of vacuolated macrophages whose contents were sudanophilic. The kidneys were not unusual. The tissue spaces of the ileal mucosa, usually occupied by round cells, were now filled with vacuolated macrophages, a few of which contained sudanophilic substance (fig. 4 *C*). The great majority, however, were sudanophobe. The substance was isotropic. The glands themselves did not appear

unusual. There was no dilatation or indication of obstruction of lymphatics in the wall of the organ. Numerous sections of mesenteric lymph nodes revealed a structure no longer resembling the normal organ (fig. 6 *C*). Lymphoid follicles were absent, and the small cysts in scarlet red preparations were seen to be filled with fat and crystals (fig. 5 *C*). The stroma consisted largely of lymphocytes with numerous eosinophilic leukocytes and only very occasional macrophages. There was no increase in the connective tissue of the organ. The large fat-filled spaces were lined in part by macrophages and in part by giant cells of the foreign body type. No dilated lymphatics could be seen about the structures. The fibrous capsule of the lymph nodes likewise contained numerous lipoid droplets, which were arranged in linear form similar to that seen wherever macrophages break down within fibrous tissue spaces.

The diagnoses were intestinal lipodystrophy; cachexia; endocardiosis of the tricuspid valve; aspiration lobular pneumonia of the lower lobes of both lungs; fibrous pericarditis; pleural adhesions; fibrous perisplenitis, and acute passive visceral congestion.

CASE 4.—A white male farmer aged 33 was admitted on Oct. 16, 1935, with a complaint of loose stools for two and one-half months. His father was living but had hypertension, and his mother was said to have pellagra. The past history was noncontributory. About fifteen months before admission the patient began to have chills and fever which occurred one to three times a week. Soon after the onset of these symptoms he noted pain, stiffness and swelling in the joints, beginning in the hands and migrating to most of the other joints in turn.

A diagnosis of malaria was made on several occasions after examination of blood smears, and the patient received three courses of quinacrine hydrochloride U. S. P. (atabrine dihydrochloride®), quinine to the point of temporary deafness and two courses of injections (probably arsenic). Apparently there was some improvement following each course of therapy but the relation of this improvement to treatment was uncertain. Shortly after the third course of quinacrine and about two and one-half months before admission there was onset of diarrhea with three to six stools a day. For the first few days dark and fresh blood was present in the stools, with occasional blood thereafter. Usually, however, the stools were said to resemble soapsuds, were large and foamy and contained mucus. There was considerable colicky abdominal pain, worse at the time of defecation. Before the onset of his illness the patient's weight was 173 pounds (78.5 Kg.), just before the onset of diarrhea 160 pounds (72.6 Kg.) and at the time of admission 143 pounds (64.9 Kg.).

The temperature on admission was 38.3 C. (101 F.) and it ran a spiking, septic course during the almost eight weeks of hospitalization, with elevations to 38 to 39 C. (100.4 to 102.3 F.) on all except a few days. The blood pressure was 102 systolic and 60 diastolic. Significant physical findings were slightly enlarged epitrochlear lymph nodes, inflammation of the tonsils and tenderness in the epigastrium and left lower quadrant of the abdomen. No masses or organs could be felt in the abdomen. Proctoscopic examination showed only some edema and hyperemia of the rectal mucosa.

The hemoglobin was 11.3 Gm. per hundred cubic centimeters (73 per cent), erythrocytes 3,800,000 and leukocytes 4,000; the differential formula was normal. Urinalyses showed normal conditions except for a few red blood cells in one specimen. Benzidine tests for occult blood in stools elicited strongly positive reactions; ova or parasites were not found. Determination of fat was not done. Repeated stool examinations failed to demonstrate amebas or cysts. Stool cultures were negative for organisms of the typhoid–dysentery group, Brucella organisms

and hemolytic streptococci. The Widal reaction was negative. Serologic reactions for syphilis were negative. Gastric analysis showed no free hydrochloric acid and 27 degrees of total acid in the fasting content and 71 and 86 degrees respectively after injection of histamine. The blood nonprotein nitrogen was 28 mg., plasma proteins 5.5 Gm. (albumin: globulin ratio 1.0), serum calcium 8.6 mg. and phosphorus 5 mg. per hundred cubic centimeters. Brucella agglutination tests were negative, and the van den Bergh reaction was normal. Blood cultures, including special technic for Brucella organisms, showed no growth.

The gallbladder was not visualized roentgenologically after oral ingestion of dye, although there was some possibility that it might have been obscured by gas and dye in the colon. A barium sulfate enema filled the colon well except at the base of the cecum, which seemed spastic. There was some tenderness over this area and over the sigmoid area. Amebic colitis was suspected. Serial examinations of the gastrointestinal tract after a barium sulfate meal showed pronounced hypomotility throughout the small intestine, with occasional dilated loops. At six hours, however, the ileum was almost empty of barium but several loops were distended with gas. Nothing abnormal was seen in the cecum at this time. It was felt that the findings were indicative of generalized adhesions, probably due to some inflammatory process in the ileum. The lungs were clear on roentgen examination.

The patient was given a high calory low residue diet with supplementary vitamins and iron. He received a course of carbarsone without benefit. The anemia failed to improve at first, and hence two blood transfusions were given. There was some abdominal discomfort with occasional cramps accompanying the diarrhea. However, the stools gradually decreased in number with symptomatic treatment. The temperature continued to rise almost daily. About one month after admission the cramps abruptly became severer, the blood pressure dropped to about 90 systolic and the patient passed several large tarry stools. Fluids were given intravenously, with recovery of the blood pressure. After this episode and with the administration of iron and liver extract by mouth, the blood picture gradually improved so that the hemoglobin reached 12.5 Gm. per hundred cubic centimeters (82 per cent) and the red cells 4,800,000. However, the daily elevation of temperature persisted, as did occult blood in the stools. After two months in the hospital the patient was discharged, somewhat improved, but without a definite diagnosis. The presumptive diagnosis was chronic idiopathic ulcerative colitis, but it was felt that there might be a cancerous condition of the small bowel.

The patient was directed to continue the same program at home and to return in one month for reexamination. However, he was brought to the emergency ward about three weeks after discharge, and it was stated that during the previous week or two at home his symptoms had become worse, with increasing weakness, pallor and dyspnea. The dyspnea was severer on his arrival in the emergency ward, and the patient died before he could be put to bed. It was suspected that death was due to shock from internal hemorrhage.

Autopsy.—The body was that of a well developed but emaciated white man approximately 35 years of age and 176 cm. in length. The weight was estimated at 115 pounds (52.1 Kg.). No nodules were palpable in the neck, axillas or groin.

On exposure of the peritoneal cavity neither adhesions nor free fluid was seen. The intestines were moderately distended, as was the stomach. The omentum and mesentery contained a moderate amount of fat.

Each pleural cavity contained approximately 150 cc. of clear pale yellow fluid. There were no adhesions, and the pleural surfaces were smooth and glistening

throughout. The pericardial cavity was filled with approximately 400 cc. of clear yellow fluid. There were no adhesions, and the serosal surfaces were smooth and glistening.

The heart weighed 350 Gm. and showed no recognizable lesions.

The right lung weighed 720 Gm. and the left 510 Gm. The two were essentially similar in appearance. In the lower lobes were small discrete areas which were firmer than the surrounding tissue, somewhat raised above the cut surface and dark purple to red.

The liver weighed 2,120 Gm.; it and the gallbladder appeared normal. The extrahepatic bile ducts were patent throughout. The pancreas weighed 100 Gm. and the spleen 140 Gm.; neither was unusual in appearance.

Except for superficial ulceration in the distal third of the esophagus, this portion of the gastrointestinal tract was not remarkable. A similarly superficial, but much smaller, ulcer was found in the midregion of the posterior wall of the stomach near the cardiac end; it measured about 3 mm. in diameter. The mucosa was otherwise normal in all respects. Throughout the entire small intestine the mucosa was unbroken but marked by multitudes of closely situated pale gray to grayish yellow spots, which lent the surface a finely strippled velvety appearance. The plicae of the duodenum and jejunum were thickened. The mesenteric lymph nodes were very numerous and enlarged. They measured up to 1.5 cm. in diameter, were firm and on section showed a pale, greenish tan appearance. The appendix was not unusual. The large intestine contained semifluid, dark green feces. The mucosa was not unusual, and the wall was not thickened.

The combined weight of the adrenal glands was approximately 20 Gm. They were not unusual in appearance.

Each kidney weighed 140 Gm. The capsules stripped with ease, revealing smooth red-brown surfaces. The cortices averaged 5.0 mm. in thickness, and normal architecture was clearly visualized. The pelves, ureters and urinary bladder were likewise not remarkable.

The aorta throughout its course showed only small atheromatous plaques. The periaortic abdominal lymph nodes were large and firm and presented pale greenish tan cut surfaces similar to those of the mesenteric nodes.

Bone marrow from vertebrae and a femur was dark red and moist in appearance. The brain showed no unusual changes, and the pituitary gland was small, firm, symmetric and approximately 8 mm. in diameter.

Microscopic Examination.—The myocardial fibers were somewhat vacuolated. Aside from this there were no visible changes in the heart.

Sections from both lungs were characterized by the presence of pulmonary edema and numerous macrophages; these were vacuolated. Sudan stain revealed that the vacuoles were composed of sudanophilic material, undoubtedly the result of aspiration of fatty substances. There were numerous small groups of alveoli which were filled with exudate consisting largely of fibrin and a few leukocytic round cells. These exudates were in the process of organization. Some already had undergone complete organization, presenting characteristic hourglass figures. In still other areas the pneumonia was rather fresh.

The liver was marked by the presence of central areas of necrosis. These foci were extensive and involved almost every lobule. They were characterized by the presence of numerous polymorphonuclear leukocytes about and between the necrotic cells. The midzonal and peripheral portions of the lobules were, however, still more or less intact except for the presence of numerous fat vacuoles. The portal fields showed no unusual changes.

The wall of the gallbladder was completely normal in appearance. The villi were typical in size and shape, but the epithelium had been lost through autolysis. The pancreas showed an essentially normal architecture. The islets were numerous and normal in appearance.

The spleen showed two interesting changes: one, numerous foci of hemopoiesis, and the other, small collections of vacuolated macrophages (fig. 5*D*) associated with lymphoid follicles. There were numerous foci of iron-containing pigment within macrophages.

The adrenal and pituitary glands were not unusual. The aorta showed no abnormal changes. The kidneys and prostate gland showed completely normal appearance; however, study of the testis revealed that spermatogenesis had halted at the stage of spermatogonia.

The femoral marrow was very active. There was relatively little fat, and numerous blood cells of all types were recognized, including numerous megakaryocytes. The vertebral marrow was likewise active.

The esophagus showed shallow ulcerations whose bases were composed of necrotic tissue and numerous polymorphonuclear leukocytes. Scattered about within the submucosa and between the muscle bundles were many round cells, chiefly lymphocytes, monocytes and plasma cells. An occasional small vessel showed fresh thrombosis. The stomach was normal in all respects. However, as examination progressed from the pylorus into the bulb of the duodenum, one saw, a few millimeters beyond the pyloric ring, occasional large macrophages, which increased in number caudad. The jejunum revealed focal collections of these large foamy macrophages within the tips of villi. However, in the ileum the entire submucosa was composed solely of glands lined with normal-appearing epithelium and between these structures masses of macrophages (fig. 4*D*). They were all vacuolated, and many appeared to contain highly refractile bodies. These not only were in the tips of the villi but were found in the propria down to the muscularis mucosa. They were not seen, however, beyond this limiting membrane.

The phagocytosed material was nonsudanophilic and isotropic. Occasional cells contained lipid in the form of sparse or packed droplets. In the hematoxylin and eosin preparations were scattered small round spaces, some in the villi, others between these structures and still others close to the muscularis mucosae. They were not lined by endothelium, and sudan IV stain revealed their contents to be intensely sudanophilic.

In the submucosa, muscularis and subserosa there was no evidence of dilated lymphatics. The lymph nodes of the mesentery were completely atypical in architecture (fig. 6*D*). They contained numerous large and small, round and oval-shaped spaces, which with sudan IV stain revealed themselves to be filled with fat and fatty acid crystals. Surrounding these areas were macrophages which showed foamy cytoplasm and an occasional giant cell. The stroma between these large globules of fat was composed of lymphocytes, plasma cells, occasional eosinophilic leukocytes and groups of macrophages showing the same characteristics as those surrounding the fat. These were not within the sinusoids but rather were in the parenchyma of the organ. The surrounding capsule was composed of fibrous tissue and was not unusually thickened. The mesenteric fat within which the lymph nodes lay was infiltrated by lymphocytes, plasma cells, occasional eosinophilic leukocytes and monocytes. Again, there was no evidence of lymphatic obstruction.

The diagnoses were intestinal lipodystrophy; chronic passive visceral congestion; hydropericardium (400 cc.); bilateral hydrothorax (150 cc.); diffuse centrolobular hepatic necrosis; subacute and organizing focal pneumonia; acute ulceration of the terminal portion of the esophagus and acute ulcer of the stomach.

COMMENT

The literature arising about Whipple's disease still is largely concerned with case reports. Since considerable effort now is being made to discover and investigate the condition before death, a number of more than doubtful examples of the disease have been introduced into the literature. As a result, it appears desirable to redefine the disease.

Table 1 summarizes the pertinent data from the history, clinical findings and autopsy study of 23 reported cases. These have been divided into three categories: Group 1 encompasses 15 cases which we consider to be authentic examples of Whipple's disease: group II, 4 instances of chylous obstruction and its sequelae, and group III, 4 nonfatal cases which seem to be examples of other disease processes.

Most of the confirmed cases of Whipple's disease have been recognized in this country. However, other cases have been reported from England, Germany and South America. With only 15 proved cases in the literature, it seems noteworthy that 4 were found in North Carolina. All 4 of the patients were born and lived the greater part of their lives in the state. Whether this geographic incidence is due to environmental factors or merely to fortuitous circumstances remains to be seen.

The 4 cases reported in this paper have marked similarities in history, clinical findings and pathologic anatomy. All the patients were white men between the ages of 33 and 56. Their gastrointestinal symptoms followed a fairly uniform pattern with abdominal discomfort, dyspepsia and diarrhea. The time of onset of these symptoms varied from one-half to three years before death but was about one year in 2 of the 4 cases. The evidence of failure of intestinal absorption with extreme cachexia was striking in each case. All patients complained of chronic arthritis; 3 of the 4 had a chronic cough, and all gave a history of malaria. In none was a significant pulmonary disease demonstrated during life. One of the patients had progressive renal disease. The pathologic anatomy was almost uniform in all 4 cases.

That many points of similarity extend beyond our series to the entire group of confirmed cases will be evident from the data in table 1, group I. Thus all the patients were men, aged 27 to 60. A history of arthritis was mentioned in 12 of the 15 and is denied in 1. Whipple [1] and Sailor and McGann [3] referred to chronic cough in their patients, but the recorded histories are not sufficiently complete in most cases to judge the frequency of this symptom. The duration of gastrointestinal symptoms in most of the cases was similar to that observed in

3. Sailor, S., and McGann, R. J.: Lipophagic Granulomatosis of the Enteric Tract, Am. J. Digest. Dis. **9**:55-63, 1942.

TABLE 1.—*Summary of Data from 23 Reported Cases of Intestinal Lipodystrophy**

	Group I†															Group II				Group III			
	Whipple [1]	Fleischmann [4]	Jacobo [12a]	Hill [12b]	Glynn and Rosenheim [12c]	Korsch [6]	Sailor and McGann [8]	Apperly and Copley [13d]	Vaux [12e]	Esteudero [12f]	Amsterdam and Grayzel [13g]	Our Case 1	Our Case 2	Our Case 3	Our Case 4	Blumgart [9] Case 2 ‡	Reinhardt and Wilson [14]	Fitzgerald and Kinney [10]	Rosen and Rosen [11]	Pearse [6]	Pemberton [7] Case 1	Pemberton [7] Case 2	Pemberton [7] Case 3
Sex	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	F	M	M	F	M	M	F	F
Age	36	38	37	60	44	60	45	31	49	27	54	56	52	45	33	44	74	48	54	59	65	62	58
Duration of symptoms (yr.)																							
Arthritis	5	..	15	..	..	10	5	4	..	1	..	6	?	4	1½	..	..	..	..	13	..	..	17
Abdominal symptoms	½	½	2	1	1	1	½	4	9	1	2	1	3	1	½	2	1	1	½	15	¼	½	..
History																							
Abdominal discomfort	?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+
Asthenia, weight loss	+	+	..	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	..	++	..	0
Diarrhea	+	..	+	+	+	+	?	+	+	+	+	+	+	+	+	0	?	+	+	..	+	+	0
Blood in stools	..	..	+	..	+	0	+	?	0	+	+	+	+	0	+	+?	..	0	0	..	..	..	0
Fever	+	+	+	0	0	+	0	..	0	+	+	0	+	0	+	0	..	+	0	..	..	..	..
Arthritis	+	+	+	..	..	+	+	+	+	+	0	+	+	0	+	0	0	0	0	+	0‡	0	+
Chronic cough	+	..	..	..	..	..	+	..	..	..	..	+	+	..	..	..	..	+	..	..	0‡	0	..
Clinical Findings																							
Skin pigmentation	+	0	+	..	+	0	+	..	±	+	+	+	0	0	..	0	..	..	+	..	0§	..	..
Hypotension	..	..	..	+	+	..	+	+	..	+	+	+	+	+	+	0	..	..	±	0	0	0	..
Edema	..	..	..	..	..	0	+	+	..	+	+	+	..	..	+	0	+	+	+	0	0	..	..
Anemia	+	0	+	+	+	+	+	+	+	..	+	+	+	+	0	+	+	+	+	0	0	0	0
Leukocytosis	0	..	0	0	+	0	+	0	0	0	+	0	±	0	0	0	+	+	+	0	+	0	0
Eosinopbilia	+	..	..	0	..	..	..	+	0	0	0	+	±	0	0	..	0	0	0	0	..	..	..
Hypoproteinemia	..	..	..	..	..	..	+	..	..	+	+	+	0	+	0	..	..	..	0	0	0	0	0
Hypocalcemia	..	..	..	..	..	..	..	..	..	+	0	+	..	+	±	+?	..	..	0	..	0	0	0
Achlorhydria	..	..	0	..	0	..	+	+	0	+	..	0	+	0	0	..	..	..	..	0	0	0	0
Steatorrhea	+	..	..	..	+	..	..	..	+	+	0	+	+	+?	..	0	..	..	0?	..	0	0	0
Low glucose tolerance curve	..	..	+	..	..	..	..	..	..	..	+	+	..	..	..	..	..	..	..	±	..	..	..
Pathologic Findings																							
Intestinal macrophagocytosis	+	..	+	+	+	..	+	+	+	+	+	+	+	+	+	+	..	+	+	..	..	..	..
Fat stain, intestinal macrophages	0	..	..	..	..	..	..	..	..	..	..	0	..	0	0	..	..	..	..	..	..	..	..
Mesenteric lymphatic dilatation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	..	+?	+	0
Chylous ascites	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	..	0	0	0
Fibrous pericarditis	+	+	+	+	+	+	+	0	+	0	0	0	+	+	0	0	..	0	0	..	..	..	..
Marantic endocarditis	+	0	+	0	0	+	0	0	0	+	0	+	+	+	0	0	..	0	0	..	..	..	..
Lipogranuloma, mesenteric nodes	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	..	+	+	+	..	..	..	..

* Modified from Apperly and Copley and Amsterdam and Grayzel.

† After this table was prepared 3 additional case reports were published (Chapnick, H. A.: Ann. Int. Med. **29**: 549-558, 1948; Newman, B., and Pope, R. H.: Gastroenterol. **11**: 120-126, 1948; Schutz, P. J.; Benner, W. H., and Christian, W. A.: Am. J. Med. **7**: 553-563, 1949). The last-mentioned is a thoroughly studied case which should be classified in group I; the other 2 probably belong in the same category. All patients were men.

‡ This patient had an attack of arthritis at age 16.

§ "Physical examination revealed only an indefinite . . . mass in . . . the abdomen."

¶ Leukemia?

our patients. Steatorrhea has been recognized in 7 of the 15 and denied specifically in only 1. Anemia has been present uniformly, and hypotension and pigmentation of the skin have been noted frequently.

Although the clinical picture in these cases is reasonably uniform, the symptoms and findings are by no means pathognomonic. Thus there are many points of similarity to the sprue syndrome. On the other hand, the pathologic lesions and their distribution are characteristic and furnish the criteria for classification in table 1 of those cases which we consider instances of Whipple's disease. The impression is gained from the study of these data that we are dealing with a definite disease entity.

Two positive lesions and one which is absent characterize the disease. The more prominent of the two is lipogranulomatosis of the mesenteric and draining lymph nodes (figs. 3 and 6). The second is macrophagocytosis of the lamina propria of the small intestine (fig. 4) and occasionally of the proximal portion of the colon (case 1). The consistent absence of significant anatomic evidence of obstructed lymphatics, such as dilated lymph vessels, chyle cysts and ascites, is a most significant negative finding. It also is worthy of note that fibrous pericarditis and marantic endocardiosis were frequently reported in the confirmed cases but were not mentioned in any of the doubtful ones.

Excepting the cases of Fleischmann [4] and Korsch,[5] in which the lamina propria of the intestine appears to have been overlooked, all the cases of group I fulfil the anatomic criteria. Despite the seriousness of the omission in these 2 cases, the changes in mesenteric lymph nodes and the clinical histories are so typical that they have been retained.

The 4 cases of group II are segregated, since on analysis they appear to be examples of chylous obstruction which differ in many important respects from those of group I. Pearse's case [6] and those of Pemberton and associates,[7] group III, are considered to be instances, respectively, of peritoneal lipogranulomatosis and mesenteric xanthomatosis.

It is necessary at this point to explain the absence from table 1 of 3 cases usually cited in the literature. In Blumgart's case 1 [8] the characteristic lesions of Whipple's disease were not described. Case 3

4. Fleischmann, R.: Ueber tumorbildende Fettgewebsgranulome im Gekröse des Dunndarms, Arch. f. klin. Chir. **158**:692-701, 1930.

5. Korsch, H. J.: Fettstoffwechselstörung mit Granulombildung im Mesenterium, Zentralbl. f. allg. Path. u. path. Anat. **71**:337-344, 1938.

6. Pearse, H. E.: Whipple's Disease, or Intestinal Lipodystrophy, Surgery **11**: 906-911, 1942.

7. Pemberton, J. deJ.; Comfort, M. W.; Fair, E., and Zaslow, J.: Intestinal Lipodystrophy (Whipple's Disease), Surg., Gynec. & Obst. **85**:85-91, 1947.

8. Blumgart, H. L.: Three Fatal Adult Cases of Malabsorption of Fat, Arch. Int. Med. **32**:113-128 (July) 1923.

was inadequately described; and, since the same may be said of Boeck's report,[9] it appears best to eliminate all 3 from serious consideration.

Group I.—Little is to be gained by a review of the various theories of the etiology and pathogenesis of Whipple's disease, all of which are adequately discussed in recent publications.

So far as we are aware no experimental approach to the problem of the pathogenesis of the disease has been reported. However, Stryker [10] in 1941 published the results of a study of the absorption of liquid petrolatum in rabbits, and examination of his work reveals that he produced lesions in his animals comparable to, but not identical with, those of Whipple's disease.

The animals were fed a stock diet plus liquid petrolatum for periods up to thirteen months, and in those kept on this program for longer than seven months lipogranulomatosis of the mesenteric nodes developed. In addition, the intestines, largely jejunum and proximal portion of the colon, showed accumulation of lipophages and extracellular sudanophilic substance in the lamina propria. There is no mention of dilated or obstructed lymphatics or of chylous ascites. The identity of the fat in the tissues was established by physical and chemical tests as paraffin hydrocarbons.

Supporting Stryker's work is the evidence of Channon and Collinson,[11] who demonstrated in chemical detail the absorption of liquid petrolatum from the intestine of rats and 1 pig. More recent work by Frazer and his associates [12] has proved that liquid petrolatum may be absorbed with as much ease and speed as olive oil, provided it is properly emulsified. Unsplit fats are absorbed when reduced to particles 0.5 micron or less in diameter. Hydrolyzable fat is readily emulsified to this degree because it supplies the fatty acid and monoglyceride which, with bile salts, furnish the emulsifying system. The same workers have expressed the belief that nonhydrolyzable fats are absorbed through the chyle system, whereas hydrolyzed products (fatty acid–bile salt complexes) pass directly into the portal circulation.

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9. Boeck, W. C., in discussion on Bargen, J. A.; Bollman, J. L., and Kepler, E. J.: The Diarrhoea of Pancreatic Insufficiency, Am. J. Digest. Dis. & Nutrition **4**:728-732, 1938.

10. Stryker, W. A.: Absorption of Liquid Petrolatum ("Mineral Oil") from the Intestine: Histologic and Chemical Study, Arch. Path. **31**:670-692 (June) 1941.

11. (*a*) Channon, H. J., and Collinson, G. A.: The Unsaponifiable Fraction of Liver Oils: V. The Absorption of Liquid Paraffin from the Alimentary Tract in the Rat and the Pig, Biochem. J. **23**:676-688, 1929. (*b*) Stetten, DeW., Jr.: Metabolism of a Paraffin, J. Biol. Chem. **147**:327-332, 1943.

12. (*a*) Frazer, A. C.; Schulman, J. H., and Stewart, H. C.: Emulsification of Fat in the Intestine of the Rat and Its Relationship to Absorption, J. Physiol. **103**:306-316, 1945. (*b*) Frazer, A. C.: Aetiology of Steatorrhoea, Brit. M. J. **2**:641-645, 1947.

As previously mentioned, the lesions produced by Stryker in rabbits were not identical with those of Whipple's disease. The substance demonstrated by Stryker in the mucosal macrophages and mesenteric lymph nodes of animals with "paraffinoma intestinalis" was liquid petro-

TABLE 2.—*Analysis of Intestinal Mucosa of Cases 1 and 3 (Whipple's Disease) and a Control Case (Chronic Myelogenous Leukemia)*

	Case 1		Case 3		
	First Analysis	Second Analysis	First Analysis	Second Analysis	Control
Wet weight	15.24 Gm.	14.6 Gm.	15.15 Gm.	14.4 Gm.	14.9 Gm.
Weight of lipids	0.344 Gm.	0.233 Gm.	0.337 Gm.	0.255 Gm.	0.144 Gm.
Per cent of lipids	2.26	1.60	2.22	1.79	0.97
Free fatty acids	0.080 Gm.	0.009 Gm.	0.007 Gm.	0.011 Gm.	0.004 Gm.
Soap fatty acids	0.073 Gm.	0.063 Gm.	0.063 Gm.	0.054 Gm.	0.025 Gm.
Total cholesterol	0.049 Gm.	0.042 Gm.	0.044 Gm.	0.034 Gm.	0.062 Gm.
Free cholesterol	0.008 Gm.	0.030 Gm.	0.027 Gm.	0.024 Gm.	0.026 Gm.
Phospholipids	0.019 Gm.	0.013 Gm.	0.012 Gm.	0.011 Gm.	0.01 Gm.*
Phospholipids, per cent of tissue	0.124	0.09	0.08	0.07	0.07
Phospholipids, per cent of lipids	7.0	5.7	4.3	4.3	7.1
Neutral fat	0.172 Gm.	0.074 Gm.	0.206 Gm.	0.135 Gm.	0.067 Gm.
Neutral fat, per cent of tissue	1.13	0.51	1.35	0.94	0.44
Neutral fat, per cent of lipids	50	32	62	53	47
Nonsaponifiable matter	0.068 Gm.	0.054 Gm.	0.061 Gm.	0.046 Gm.	0.042 Gm.

* The low phospholipid values, as is indicated by the control values, are not considered significant. It is possible that the tissue preservative (Kaiserling fluid) may be responsible for the low values.

TABLE 3.—*Analysis of Mesenteric Lymph Nodes of Cases 1 and 3 (Whipple's Disease)*

	Case 1		Case 3	
	Grams	Percentage of Lipid	Grams	Percentage of Lipid
Wet weight of specimen	14.2	....	14.7	....
Total lipid	4.515	....	3.219	....
Total fatty acids	3.06	68	2.042	64
Total fatty acids, molecular weight	310	....	284	....
Free fatty acids	0.306	6.7	0.335	10.4
Soap fatty acids	0.158	3.5	0.177	5.4
Soap fatty acids, mean molecular weight	324	....	320	....
Total nonsaponifiable	0.55	12.2	0.240	7.5
Ester cholesterol	0.451	....	0.221	....
Free cholesterol	0.058	....	0.067	....
Nonsaponifiable, noncholesterol	?	....	?	....
Phospholipid	0	....	0	....
Neutral fat (approximate)	.....	78	.....	77

latum by chemical tests and was sudanophilic. In contrast, the intestinal macrophages of Whipple's disease when appropriately stained are almost all nonsudanophilic, and the intestinal mucosa in our cases 1 and 3 did not contain, by chemical analysis, liquid petrolatum or increased amounts of recognizable lipid material (tables 2 and 3). In this respect attention is directed to the fact that, aside from 3 of our cases, there is only 1 other instance of a definitive statement regarding the fat-staining properties of these peculiar intestinal macrophages. Whipple [1] found that they did not stain with osmic acid (table 1). The chemical analysis of lymph

nodes of our cases 1 and 3 (table 3) also failed to reveal any unusual lipid material such as liquid petrolatum.

The similarity of the lesions produced by Stryker to those of Whipple's disease is impressive and has been overlooked in the past. This work does demonstrate that the absorption of a foreign lipid such as liquid petrolatum can produce comparable lesions, and Whipple [1] suggested in his original paper that the absorption of such a substance might be the cause of the condition he described. However, if this is the case, neither he nor any of the other writers, including ourselves, have been able to identify the offending substance or substances.[12a]

A factor of importance, although of negative value, is the absence of evidence indicating that Whipple's disease is the consequence of qualitatively or quantitatively inadequate production of pancreatic enzymes. Our case 1, which is among the more completely studied instances of Whipple's disease in the literature, supports this view. Duodenal secretion contained ample amounts of lipase, diastase and trypsin.

Fibrous pericarditis was reported in 10 of the 15 cases of Whipple's disease. While in numerous instances mention is made of pleural and peritoneal adhesions, evaluation of these statements is fraught with insecurity. The existence of all but very pronounced abdominal and pleural adhesions is frequently not noted in autopsy protocols; furthermore, many of the patients were subjected at one time or another to laparotomy. Such procedures may result in abundant adhesion formation. It therefore appears best to confine interest to the pericardium. An incidence of 66 per cent of fibrous pericarditis in so small a group is startling. In addition, 12 of 13 patients gave a history of arthritis preceding the onset of gastrointestinal symptoms. Of these 12, in 8 the arthritis was noted from one to five years before death. In 2 others it antedated death by, respectively, ten and fifteen years. The time relationships of the remaining 2 are not stated in the reports. It is probable, therefore, that a systemic disease involving joints, pericardium and, possibly, the pleura and peritoneum preceded in many instances the onset of the disease and may be an essential feature of its pathogenesis.

The extracellular fat in the intestinal lamina propria (fig. 4 *B*) is possibly an index of chylous obstruction; however, the absence of other evidence such as will be described in the 4 cases of group 2, table 1, is significant. Complete or marked chylous obstruction in the presence of normal absorption of fat leads to grossly visible dilatation of the lymphatics, formation of chyle cysts and chylous ascites. In none of the 15

12a. Work by one of us after this manuscript was submitted for publication has identified the nonsudanophilic isotrophic substance in the macrophages of the intestinal mucosa and the mesenteric lymph nodes as glycoprotein (Black-Schaffer, B.: The Tinctoral Demonstration of a Glycoprotein in Whipple's Disease, Proc. Soc. Exper. Biol. & Med. **72**:225-227 [Oct.] 1949).

instances of Whipple's disease was this true. It is apparent, then, that either the obstruction is very mild or the absorption of fat by the intestinal epithelium is so inadequate as to fail to produce lesions of chylous obstruction.

It is known from numerous clinical studies [13] that fat absorption is inadequate. Therefore, of the two possibilities mentioned, that of epithelial failure to transmit fat is, most probably, the physiologic source of this aspect of Whipple's disease. In addition, the low glucose tolerance test values indicate a fault in carbohydrate absorption similar to that in sprue and presumably referable to the enteric epithelium.

The fecal fat analysis of our case 1 showed an extraordinarily high value for fat (59 per cent by dried weight, of which 80 per cent was fatty acids and soaps). In case 2 the figure for the only similar examination was 56 per cent. This is incontrovertible evidence of inadequate fat absorption. According to Frazer,[12] emulsification of nonhydrolyzed fats occurs in the duodenum at a p_H of approximately 6.4. In this milieu relatively little lipase effect is demonstrable, but absorption of some of the unhydrolyzed fat does occur. The unabsorbed fat must then pass on to the distal part of the small intestine (p_H 8.0 or more), where the lipase is more effective, and there the fatty acids are produced. The fact that these are excreted in the stool in Whipple's disease indicates a fault in their absorption.

There is no reason to suspect the presence of unusual foodstuffs in the diets of persons in whom intestinal lipodystrophy develops. Hence it is postulated that, in association with a generalized disease of unknown nature (polyserositis), gastrointestinal function is deranged, resulting in the gradual accumulation in the mucosa of macrophages filled with material of unknown chemical nature,[12a] which does not take the usual fat stains and is not a steroid or a phospholipid. The same phagotaxic substance is likewise present in the mesenteric lymph nodes (fig. 5 *B*). The identical localization of phagocytosed liquid petrolatum in intestinal paraffinoma [10] suggests that the unidentified substance follows the same route as nonhydrolyzed fats [12] on their way from enteric lumen to thoracic

13. (*a*) Jarcho, S.: Steatorrhoea with Unusual Intestinal Lesions, Bull. Johns Hopkins Hosp. **59**:275-290, 1936. (*b*) Hill, J. M.: Mesenteric Chyladenectasis, Am. J. Path. **13**:267-276, 1937. (*c*) Glynn, L. E., and Rosenheim, M. L.: Mesenteric Chyladenectasis with Steatorrhoea and Features of Addison's Disease, J. Path. & Bact. **47**:285-290, 1938. (*d*) Apperly, F. L., and Copley, E. L.: Whipple's Disease (Lipophagia Granulomatosis), Gastroenterology **1**:461-470, 1943. (*e*) Vaux, D. M.: Chyladenectasis (Mesenteric) with Steatorrhea, J. Path. & Bact. **55**:93-96, 1943. (*f*) Escudero, P.; Mosto, D., and Landabure, P. B.: Lipodistrofia intestinal de Whipple, Trab. cient. d. Inst. nac. nutrición (1942-1943), 1944, pp. 549-572. (*g*) Amsterdam, H. J., and Grayzel, D. M.: Intestinal Lipodystrophy (Lipophagic Granulomatosis or Whipple's Disease), Am. J. M. Sc. **210**:605-611, 1945. (*h*) Whipple.[1] (*i*) Sailor and McGann.[3] (*j*) Fleischmann.[4] (*k*) Korsch.[5]

duct. Once in the mesenteric nodes, the visibly strongly phagotaxic substance elicits a reaction similar to that in the intestine. The macrophages thus mobilized engulf any other suitable material available—in these sites, fats. The lipid, available in larger amounts to the phagocytes, eventually dominates the picture, resulting in lipogranulomatosis. Such a pathogenesis of the visible lesions of Whipple's disease is supported by the presence of numerous instances (illustrated in our series by cases 1, 2 and 4) of extracellular globules of sudanophilic substance in the intestinal mucosa as well as in some of its macrophages. These observations indicate that some nonhydrolyzed fat is still being absorbed, thus accounting for the slowly progressive lipogranulomatosis of the lymph nodes, previously outlined.

From the available information no statement can be made as to the nature or origin of the phagotaxic substance.[12a] The determination of its nature, origin and relationship to the earlier systemic polyserositis is essential to further understanding of the etiology and pathogenesis of this disease. It is probable that the presence of this substance is due to a fault in the enteric epithelium, which also leads to failure of absorption of nonlipid nutritive materials and eventual starvation of the individual.

Failure of intestinal absorption, probably indicating deranged cellular function, is typical of sprue and also is seen in other conditions. However, Whipple's disease differs strikingly from sprue in that no confirmed case has shown macrocytic anemia. Furthermore, the typical anatomic changes are not found in sprue. The functional defect in absorption in sprue probably is different from that in Whipple's disease because the former seems to be due to a deficiency state which may be corrected by adequate treatment with liver extract or folic acid. So far as we know the latter substance has not been given to a patient with Whipple's disease, but massive therapy with all types of liver extracts was to no avail in our case 1.

This leaves, then, a defect of the function of the vital absorptive membrane of the intestine, this defect being of entirely unknown nature but associated with evidence of systemic disease in the form of arthritis, pericarditis and endocarditis. There is strong indication of some type of prior infection or allergy in several of the cases, and eosinophilia was recorded in 3. This was transient and present only during the early part of the disease in our case 1. Hence, it is not unlikely that eosinophilia may have occurred in other cases when they were not under observation. There was a personal and family background of allergy in our case 1, and several of the patients complained of chronic cough. Additional pertinent data of this type may be found in other case reports, such as the mention of erythema nodosum in Whipple's patient. Eosinophilia also was recognized in this case. The patient of Apperly and Copely[12d] had urticaria and eosinophilia as well. There was history of heavy treatment

with quinacrine (atabrine®), quinine and probably arsenic in our case 4. The patient described in case 2 had taken many "headache powders" containing acetanilid and bromide.

These considerations have led us to suspect that, among other possibilities, the intestinal defect in Whipple's disease may represent an unusual form of altered reactivity or abnormal response of certain tissues to injury, perhaps by infection, perhaps by other factors. To be sure, involvement of the enteric epithelium, as in Whipple's disease, is not the usual manifestation of such altered reactivity, but lesions in the heart and arthritis may result from this cause. It also is conceivable that in some of the patients the early disturbance in the enteric tract may have led to absorption of sensitizing substances which could have produced these changes.

In addition it may well be more than coincidence that most of the patients with Whipple's disease about whom pertinent information is given showed signs suggestive of adrenal cortex insufficiency, such as increased pigmentation of the skin and hypotension. These features of Whipple's disease have been pointed out by several writers, and the patient studied by Glynn and Rosenheim [13c] "improved temporarily after the administration of cortical extract." [14] The possible relationship of the adrenal cortex to intestinal absorption [15] has been the subject of speculation in both Whipple's disease [13c] and sprue,[16] and "moderate steatorrhea" has been reported in some patients with Addison's disease.[16] It seems probable that there is a certain degree of functional injury of the adrenal cortex in Whipple's disease, probably as a part of the general disease state. However, one can conceive of such hypothetic cortical insufficiency as representing the final "stage of exhaustion" of the "adaptation syndrome" of Selye.[17]

Group II.—The 4 cases of group II (table 1) are segregated, since on analysis they appear to be examples of chylous obstruction,

14. Our patient in case 1 was similarly treated, but because of the wartime shortage of the extract, only after he was *in extremis*. There was no apparent benefit or rise in blood pressure. Sailer and McGann administered desoxycorticosterone acetate to their patient "without appreciable change." A patient described by de Groot (Nederl. Tijdschr. v. Geneesk. **90**:719, 1946) as having arthritis and manifestations of sprue and Addison's disease is said to have improved markedly after the administration of adrenal cortex extract. The clinical description of the case is very suggestive of Whipple's disease, but laparotomy was not done.

15. Verzár, F., and McDougall, E. J.: Absorption from the Intestine, New York, Longmans, Green & Co., 1936.

16. Hanes, F. M.: Sprue, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Co., Inc., 1943, vol. 4, pp. 171-196.

17. Selye, H.: The General Adaptation Syndrome and the Diseases of Adaptation, J. Allergy **17**:231-247, 289-323 and 358-398, 1946.

which differ in many respects from the 15 examples of Whipple's disease. Symptoms similar to those of Whipple's disease and the sprue syndrome are known to characterize cases of mesenteric lymphatic obstruction.[18]

From table 1 it will be noted that all 4 cases of group II showed evidence of obstruction of lymph vessels; this was seen with the unaided eye in the form of dilated mesenteric and intestinal lymphatics. Histologically the lacteals of the intestinal villi were dilated, as were the smaller lymphatics of the submucosa and serosa. The degree of lymphatic obstruction was sufficiently great to lead in 3 instances to chylous ascites —convincing proof of the ability of fats to pass the intestinal wall. In sharp contrast, none of the 15 patients with clearcut Whipple's disease showed significantly dilated intestinal or mesenteric lymph vessels or chylous ascites.

A second and no less important difference may be found in the mesenteric lymph nodes. Study of the photomicrographs of Reinhardt and Wilson,[19] Fitzgerald and Kinney,[20] and Rosen and Rosen,[21] as well as their descriptions, indicates that the principal lesion is dilatation of the lymph sinuses, both cortical and medullary. These are filled with amorphous and phagocytosed fat. There is no appreciable giant cell reaction. This situation fits the presence of generalized lymphatic obstruction which characterizes all 4 cases. On the other hand, the lymph node lesion in our 4 cases of Whipple's disease presented itself not as simple obstruction and its sequelae but rather as full-blown lipogranulomatosis with obliteration of the cortical and medullary sinuses and the ultimate destruction of normal structure accompanied with characteristic "foreign body giant cell" reaction.

The dissimilarities of these two groups appear at first glance balanced, at least in part, by a common lesion: macrophagocytosis of the lamina propia of the intestine. The morphology of the two groups, in this respect, again is not identical. The macrophages in Whipple's disease, as the photomicrographs show (fig. 5 *A*), are uniform in size and replace almost completely the normal stromal elements down to the muscularis mucosae. In the illustrations of Fitzgerald and Kinney and the Rosens the macrophages are largely concentrated about the dilated central chyle

18. Fairley, N. H., and Mackie, F. P.: The Clinical and Biochemical Syndrome in Lymphadenoma and Allied Diseases Involving the Mesenteric Lymph Glands, Brit. M. J. **1**:375-380, 1937.

19. Reinhardt, H. L., and Wilson, S. J.: Malabsorption of Fat (Intestinal Lipodystrophy of Whipple), Am. J. Path. **15**:483-492, 1939.

20. Fitzgerald, P. J., and Kinney, T. D.: Intestinal Lipodystrophy (Whipple's Disease), Am. J. Path. **21**:1069-1090, 1945.

21. Rosen, M. S., and Rosen, S. H.: Intestinal Lipodystrophy of Whipple, Am. J. Path. **23**:433-462, 1947.

ducts, obviously ingesting escaping fat or making their way, laden, from the chyle ducts into the stroma. Supporting this interpretation is the fact that both groups of authors found the macrophages to be sudanophilic, in contrast to our observations on Whipple's disease. It would appear reasonable to interpret the macrophagocytosis in these 2 cases as simply another expression of the plainly visible obstruction of chyle flow. Reinhardt and Wilson made no mention of intestinal stromal macrophagocytosis, and Blumgart's description is incomplete.

In regard to the question of chylous obstruction in Whipple's disease only two positive statements on the patency of the thoracic duct are recorded. Whipple [1] and Sailor and McGann [8] found no obstruction. In no other case was the duct examined.

Further support of this attempt to divide the 19 cases into two groups is given by the following data: Whereas 12 of 13 patients of group 1 gave a clearcut history of antecedent arthritis and 10 of 15 showed fibrous pericarditis, all 4 of group 2 were without arthritis and 3 whose hearts were examined showed no fibrous pericarditis. In addition, all 15 of group 1 were men and of the 4 in group 2, 2 were women. Whether or not Whipple's disease is associated by more than coincidence with masculinity must await the accumulation of a larger group of cases than that now available for study.

A further difference between the two groups is the fact presented by the Rosens that lymphocytosis was present in their case and was reported in 2 other instances of "intestinal lipodystrophy". The degree of lymphocytosis was such as to have led at one time or the other to a diagnosis of lymphatic leukemia in 2 cases [22] and pseudoleukemic lymphocytosis in the third.[19] Interestingly, all 3 are in the group we have designated as group II, or cases of chylous obstruction. None of the 15 patients with Whipple's disease is reported to have shown at any time an unusual lymphocytosis. The Rosens' explanation of the lymphocytosis is that lymphocytes are normally excreted into the lumen of the enteric tract, thus maintaining a balance with production; obstruction of chyle flow, as in their case, interferes with this function, resulting in an increase of circulating lymphocytes. In this light, the absence of extraordinary lymphocytosis in Whipple's disease is readily understood, since significant evidence of obstruction is not demonstrable.

The cases in group 2 showed no evidence of a basic fault of fat absorption by the intestine. The obstruction to the flow of chyle, presumably central to the mesenteric lymph nodes, resulted, however, in lesions confusingly similar to those of Whipple's disease.

It is conceivable that in intestinal lipodystrophy gradations of fat absorption may exist, producing at times an appearance similar to that

22. Fitzgerald and Kinney.[20] Rosen and Rosen.[21]

described in the 4 cases of group 2. The anatomic and anamnestic differences of the two groups, however, plus the absence of transition cases, makes such a possibility unlikely.

Group III.—Pearse's case [6] shows a remarkable resemblance to that reported in 1941 by Cruickshank,[23] the case of a 45 year old man in whom fibrous adhesions developed after laparotomy; these eventually caused intestinal obstruction. In 1937 ½ pint (475 cc.) of "liquid paraffin" was poured into the abdomen on completion of a second laparotomy to free the intestines. The paraffin was introduced in the attempt to prevent formation of further adhesions. In August 1940, intestinal obstruction again occurred, and the patient was subjected to another operation, after which he died. The description of the abdominal serosa was essentially as follows: Numerous white nodules up to 1 cm. in diameter were scattered over the peritoneal surfaces of the small intestines, the diaphragm and the liver. Dense adhesions bound the intestinal loops into a mass. The mesentery contained tumor-like nodules measuring up to 10 by 7 cm. The nodules in the mesentery and on the serosa were cystic, contained oily material and histologically were characteristic paraffinomas. Chemical analysis of the oily substance was not carried out. Cruickshank quoted Tantini's work [24] in support of his conclusion that the introduced liquid paraffin was the cause of the oleogranuloma. Tantini inoculated liquid paraffin into the abdominal cavity of guinea pigs and observed changes identical to those noted by Cruickshank.

Pearse's case [6] may well have been an instance of peritoneal lipogranulomatosis. His patient, a 59 year old farmer, was operated on in March 1939 because of recurrent crampy abdominal pain; adhesions were released, and biopsy of unnamed tissue was reported to reveal "chronic inflammation." Absence of improvement in the postoperative condition of the patient resulted in a second operation (October 1939). At this time the intestinal loops were found matted into a solid mass. The loops, when freed, were discovered to have been bound by a gelatinous-appearing substance which, when torn, released a clear fluid. Hard, pale pink nodules were present on the serosa of the intestines, liver, omentum and parietal peritoneum. The nodules were cystic and contained a yellow oily substance. Histologically they were characteristic oleogranulomas. In January 1940 the operation was repeated, and the same cystic nodules were again seen.

Pearse was not able to examine the mesenteric nodes or the intestinal mucosa. The diagnosis of Whipple's disease was based solely on the presence of multiple oleogranulomas on the abdominal serosa. Cruick-

23. Cruickshank, A. H.: Paraffinoma of the Peritoneum, Lancet **1**:4-6, 1941.

24. Tantini, E.: Processi produttivi da olio di paraffina in peritoneo nella cavia. Arch. dello inst. biochim. ital. **7**:27-48, 1935.

shank's case and Tantini's experimental work indicate that a better diagnosis in Pearse's case might have been peritoneal lipogranulomatosis.[25]

"Intestinal Lipodystrophy (Whipple's Disease)" is the title of an article by Pemberton and associates,[7] wherein are discussed 3 interesting cases of what we believe to be mesenteric xanthomatosis. This condition has been the subject of numerous articles,[26] chiefly in the German literature, and has been encountered as an incidental finding in older people. The mesentery is thickened, and very adipose, and contains firm nodules whose centers are lymph nodes showing more or less fibrosis with no xanthomatous or lipogranulomatous changes. These are surrounded by a zone of xanthomatosis wherein no giant cells or leukocytic exudate are seen. Furthermore, no accumulations of amorphous fat within or without the lymph nodes and no intestinal lesions have been noted.

Characteristic is the arrangement of the xanthoma cells which radiate out from the central mass and may be seen as subserosal cordlike structures resembling dilated lymphatics. The descriptions of the lesions in Pemberton's 3 cases and the histopathologic illustrations all indicate that they are examples of mesenteric xanthomatosis.[27] The lesion has been ascribed to inflammation such as follows surgical trauma, peritonitis and unknown causes in adipose persons and has been considered by Thannhauser [28] as an example of localized xanthoma formation in inflammatory tissue.

While the production of oleogranulomas has been most frequently described [29] in association with the introduction into tissues of hydro-

25. Pearse in a personal communication states that he could find no indication that liquid petrolatum had been introduced intraperitoneally.

26. (*a*) Karoliny, L.: Ueber die pathologische Lipoidablagerung im Fettgewebe, Virchows Arch. f. path. Anat. **264**:305-322, 1927. (*b*) Hirsch, A.: Ueber das Vorkommen doppeltlichtbrechender Lipoide im lipomatös verdickten Mesenterien und Mesenteriallipomen, Frankfurt. Ztschr. f. Path. **10**:409-430, 1912. (*c*) Schlagenhaufer, F.: Ueber das Vorkommen fettähnlicher doppelbrechender Substanzen, Zentralbl. f. allg. Path. u. path. Anat. **18**:897-899, 1907. (*d*) Versé, M.: Ueber die Cholestearinesterverfettung, Beitr. z. path. Anat. u. z. allg. Path. **52**: 1-14, 1912.

27. Pemberton and his co-workers supplied us with material from their cases.

28. Thannhauser, S. J.: Lipidoses: Diseases of the Cellular Lipid Metabolism, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1921, vol. 4, pt. 2.

29. (*a*) Pinkerton, H.: Oils and Fats: Their Entrance into and Fate in the Lungs of Infants and Children: A Clinical and Pathologic Report, Am. J. Dis. Child. **33**:259-285 (Feb.) 1927; (*b*) Reaction to Oils and Fats in the Lungs, Arch. Path. **5**:380-401 (March) 1928. (*c*) Freiman, D. G.; Engelberg, H., and Merrit, W. H.: Oil Aspiration (Lipoid) Pneumonia in Adults: Clinicopathologic Study of Forty-Seven Cases, Arch. Int. Med. **66**:11-38 (July) 1940.

carbons and fats, several forms exist which are not produced by such mechanisms. These are exemplified by sclerema neonatorum,[30] adiponecrosis e frigore,[31] "traumatic" fat necrosis of the breast [32] and other fat tissue and Weber-Christian disease.[33]

In general, the histologic appearance of all four conditions may be characterized as oleogranuloma. Variations [34] in the type and number of reacting elements are dictated by the chemical composition of the fat, its decomposition products and possibly by the reactivity of a given patient.

Since not infrequently the central portion of mesenteric lymph nodes contain much adipose tissue, the possibility must at least be suggested that spontaneous fat necrosis in these sites may produce lipogranulomatosis. No evidence in support of this hypothesis has been found.

Elsa Petri [35] described a single enlarged periaortic lymph node which was discovered in a patient who died from a carcinoma of the tongue; the changes in the lymph node were qualitatively similar to those found in Whipple's disease. Unfortunately, the appearance of the mesenteric nodes and gastrointestinal tract was not described. This report is more or less duplicated by a case examined at Duke Hospital. A peripancreatic lymph node removed from a man who died as a result of an ulcerating squamous cell carcinoma of the esophagus was found to possess all the changes characterizing lipogranulomatosis of the mesenteric lymph nodes (fig. 7). As in Elsa Petri's case, the mesentery and intestine were not adequately examined—a fate which occasionally

30. (*a*) McIntosh, J. F.; Waugh, T. R., and Ross, S. G.: Sclerema Neonatorum (Subcutaneous Fat Necrosis), Am. J. Dis. Child. **55**:112-123 (Jan.) 1938. (*b*) Lemež, L: Beitrag zur Pathogenese der subcutanen Fettgewebsnekrose Neugeborener (sog. Sclerodermia neonatorum) an der Hand einer Kältereaktion des subcutanen Fettgewebes bei Neugeborenen und jungen Säuglingen, Ztschr. f. Kinderh. **46**:323-369, 1928.

31. Haxthausen, H.: Adiponecrosis e Frigore, Brit. J. Dermat. **53**:83-89, 1941.

32. (*a*) Lee, B. J., and Adair, F. E.: A Further Report on Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, Surg., Gynec. & Obst. **34**:521-531, 1922. (*b*) Cohen, I.: Traumatic Fat Necrosis of the Breast, J. A. M. A. **80**:770-771 (March 17) 1923.

33. (*a*) Weber-Parkes, F.: A Case of Relapsing Non-Suppurative Nodular Panniculitis Showing Phagocytosis of Subcutaneous Fat-Cells by Macrophages, Brit. J. Dermat. **37**:301-311, 1925. (*b*) Bailey, R. J.: Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), J. A. M. A. **109**:1419-1425 (Oct. 30) 1937. (*c*) Larson, C. P., and Ootkin, B. N.: Relapsing Febrile Nodular Non-Suppurating Panniculitis (Weber-Christian Disease), Am. J. Clin. Path. **11**:781-787, 1941. (*d*) Spain, D. M., and Foley, J. M.: Nonsuppurative Nodular Panniculitis (Weber-Christian's Disease), Am. J. Path. **20**:783-787, 1944.

34. Hass, G. M.: Tissue Reactions to Natural Oils and Fractions Thereof, Arch. Path. **26**:956-965 (Nov.) 1938.

35. Petri, E.: Ueber das Auftreten von Fettriesenzellen, Zentralbl. f. allg. Path. **37**:1-5, 1927.

befalls these structures. The question arises whether the two lymph nodes were from instances of unrecognized Whipple's disease. Since neither case was adequately examined, little comment can be made other than to point out the similarity of these nodes to those described by Stryker [10] in persons using liquid petrolatum. Several identical lymph nodes since have been discovered here in persons showing no other changes reminiscent of Whipple's disease and none of its clinical characteristics. In view of Stryker's observations and the work of Frazer [12] and

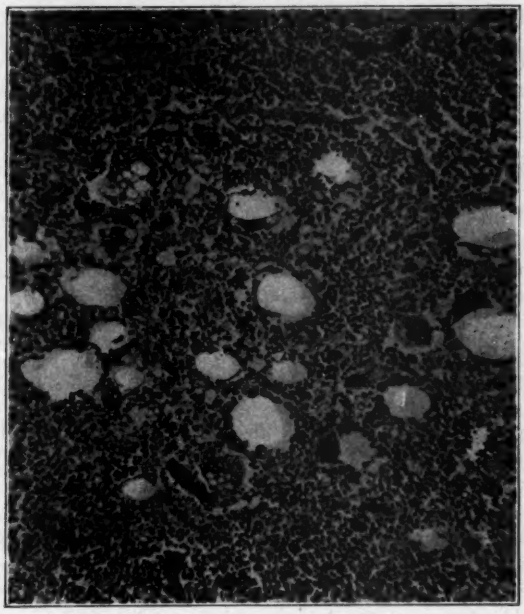

Fig. 7.—Peripancreatic lymph node of a man who died of carcinoma of the esophagus showing changes similar to, but of lesser degree than, those in lipodystrophia intestinalis. It is suspected that this represents a paraffinoma (liquid petrolatum).

his group demonstrating the ready absorbability of liquid petrolatum under certain conditions, it is very probable that Petri's and our case are examples of paraffinoma provoked by absorbed liquid petrolatum.

MANAGEMENT AND TREATMENT

It is to be hoped that cases of Whipple's disease will be recognized during life and early enough in the disease to permit thorough study. Obviously the diagnosis cannot now be made on clinical evidence alone.

However, the symptomatology is sufficiently suggestive to lead to a tentative diagnosis if the clinician is familiar with the manifestations of the disease and will keep it in mind as one of the conditions resembling sprue. Exploratory operation is indicated early in cases of "atypical sprue" which do not respond to the usual therapy. Biopsy of mesenteric nodes should be carried out because failure to do this has resulted in incorrect diagnosis during life, when the surgeon thought the gross findings indicated malignant tumor.

Unfortunately, there is no definite indication that early diagnosis will permit more effective therapy. Supportive measures will prolong life but probably will not prevent death. Trial of bile salts as used by Pearse [6] seems to be indicated, even though such medication did not produce sustained improvement in our patient (case 1). Jones and co-workers [36] recently have reported increased absorption of fat in intestinal disorders during the feeding of an emulsifying agent, polyoxyethylene sorbitan monooleate (Tween 80®). This interesting demonstration may have bearing on the treatment of Whipple's disease. Such substances should be tried when there is the opportunity to study and treat patients with the disease in the future. Roentgen therapy was reported to be of value in a presumably similar case by Boeck,[9] but there is no assurance that this patient had Whipple's disease. Adrenal cortex extract was used with temporary benefit in 1 case,[13c] but it probably never has had adequate trial. Folic acid and vitamin B_{12} deserve trial in Whipple's disease.

SUMMARY

Four new cases of Whipple's disease are reported. The diagnosis was made during life in 1 case.

Confirmed cases of the disease have been found only in men.

Whipple's intestinal lipodystrophy is characterized clinically by spruelike manifestations, usually accompanied with chronic arthritis and hypotension but without macrocytic anemia.

The disease may be recognized post mortem by nonsudanophilic macrophagocytosis of the lamina propria of the small intestine and occasionally of the proximal portion of the colon, lipogranulomatosis of the mesenteric and draining lymph nodes and absence of significant evidence of chylous obstruction.

In addition to these features, many of the patients display chronic polyserositis and marantic endocardiosis.

The cause of Whipple's disease remains unknown, but a pathogenesis is suggested.

36. Jones, C. M.; Culver, P. J.; Drummey, G. D., and Ryan, A. E.: Modification of Fat Absorption in the Digestive Tract by the Use of an Emulsifying Agent, Ann. Int. Med. **29**:1-10 (July) 1948.

It is believed that the deficient absorption of fat in Whipple's disease is due to a fault of unknown nature of the epithelium of the small intestine, which likewise impairs the absorption of glucose and perhaps of products of protein digestion as well.

It is suggested that Whipple's disease is the sequel to a systemic illness or intoxication characterized by inflammation of the serous membranes.

There is suggestive evidence in some cases of functional impairment of the adrenal cortex.

Since the diagnosis of Whipple's disease rests on the demonstration of the characteristic changes in the mesenteric lymph nodes, biopsy is imperative in order to differentiate the disease from other spruelike states.

ADDENDUM

Shortly before the proof for this paper was received we had the opportunity of observing another case of Whipple's disease in Duke Hospital. The patient was under the care of Dr. J. M. Ruffin, and diagnosis was made by exploratory laparotomy and biopsy of mesenteric lymph nodes. Extensive studies have been carried out and the patient remains under our observation.

He is a 57 year old white man, with all of the typical symptoms and findings of the disease. Deficient absorption of fat, glucose and protein hydrolysate has been demonstrated. A noteworthy finding is reduction in urinary excretion of 17-ketosteroids to 1.8 mg. per twenty-four hours (average of two determinations). Such reduction was not observed in the patient described recently by Schutz (footnote to table 1), and the determinations apparently have not been made in other cases.

At present the clinical course of the patient is satisfactory on a low fat, high protein, high carbohydrate, low residue diet with supplemental vitamins and liver extract. Emulsifying agents, and perhaps hormone therapy, will be tried if needed, and a more complete report of the case will be made at a later date.

The late Dr. Frederic M. Hanes, Professor of Medicine in Duke University, gave helpful advice in this study. His extensive knowledge of and interest in sprue and related disorders directed our attention to the study of the cases presented.

VALUE OF SOUTHEY-LEECH TUBES IN RAPID RELIEF OF MASSIVE EDEMA

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THE PURPOSE of this study is to recall to general attention a useful therapeutic measure in the treatment of massive edema, which, although in constant use in several large medical centers, has been all but forgotten by the medical profession as a whole. The mechanical removal of pleural and abdominal collections of fluid is a reputable procedure, universally used, but the relief of accumulations of fluid in the soft tissues by mechanical means is generally disdained. There are several reasons for the disrepute into which so valuable a measure has fallen. In the first place, newer concepts of the pathogenesis of edema in cardiac and renal disease have rightly directed attention toward correction of the altered physiologic processes by pharmacologic and dietetic means. Secondly, mechanical treatment of soft tissue edema was in the past followed now and then by alarming and even fatal cellulitis. With modern antibiotic drugs this serious complaint is no longer valid. Complicating infections have been abolished, in our experience, by the prophylactic use of penicillin. In the third place, the original Southey tubes sometimes drained fluid so slowly and in such small amounts, even from suitable patients, that the procedure was hardly worth while. The improved Southey tube which is the subject of this paper, however, so excels the original model that this objection no longer holds. Furthermore, unsuitable candidates have often been subjected to the procedure, with the result that the hard, brawny edema has painfully yielded but a few cubic centimeters of fluid. The prerequisite for success is that the tissues be reasonably soft and distensible. Like any other therapeutic measure, this method must be used with discretion. A final and probably paramount reason for the lack of popularity is that Southey tubes have been difficult to obtain, as we have learned from the many requests we have had for the loan of ours. Most hospitals seem not

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to have them in stock, and the large instrument companies do not make the improved model. It is hoped that this study may help to correct the scarcity.

The only ultimately reasonable treatment of edema is the removal of its fundamental cause, but rarely is this high goal attainable, except in diseases in which protein is lacking, such as starvation edema, and in beriberi, in which thiamine fills the need. More frequently the cause is not directly accessible to therapy. In heart failure, it is true, this therapeutic aim may for a while be approximated by improving the efficiency of the circulation with digitalis. Low sodium diets and mercurial diuretics may then correct the results of cardiac inefficiency, but there is often a stage in which extreme edema resists all medical measures. In similar fashion, the anasarca of the nephrotic syndrome is frequently little affected by the administration of diuretics, albumin intravenously and high protein diets. In such therapeutic straits, the physician should not scorn the immense symptomatic relief that may be afforded by the simple mechanical removal of fluid from the soft tissues. "To give comfort rather than to prolong a miserable existence" becomes in such a situation the only tenable purpose.[1]

Although mechanical measures for relieving edema have been known for centuries, they have had to be rediscovered periodically. Celsus, the medically minded Roman encyclopedist, described in about 30 A. D. the relief of dropsy by incision of the skin above the ankle.[2] Variations of his method have been employed up to the present. Acupuncture, or the making of multiple needle pricks in the skin, was in use for a century or so. In 1877, Reginald Southey, a physician of St. Bartholomew's Hospital in London, described an improvement over these crude practices. His device, demonstrated before the Clinical Society of London, was, he observed, "almost too simple to dwell upon . . . but great and useful ends are usually attained by the simplest means" [3] When confronted by a young woman who was "distended almost to bursting" with the extreme anasarca of chronic nephritis, he conceived the idea of inserting cannulas into the patient's swollen legs. The tubes were little more than modifications of the hypodermic needles then coming into general use. As a matter of fact, the idea occurred to Southey when he thought about using hypodermic needles for the pur-

1. White, P. D., and Monks, J. P.: The Grateful Relief of Scrotal Dropsy by the Use of a Southey Tube, J. A. M. A. **101**:1632 (Nov. 18) 1933.

2. Celsus, A. C.: Of the Several Species of the Dropsy, and Their Cure, in De re medica libri octo, Haganoæ, J. Secerium, 1528, book 3, chap. 21.

3. Southey, R.: Chronic Parenchymatous Nephritis of the Right Kidney, Tr. Clin. Soc. London **10**:152, 1877.

pose; he considered his instrument merely an improvement thereon.[4] Incidentally, "the wheel is come full circle," for hypodermic needles were recently proposed as substitutes for Southey's tubes.[5] With the first trial of his simple device, Southey removed an average of over 2 liters of edema fluid daily on each of six successive days.

In the half-century following Southey's announcement, his apparatus was used fairly widely in England but was forgotten in all but a few places here in America. Then, in 1930, Bland and White, having observed the excellent results obtained by Sir Thomas Lewis in London, recommended the revival of Southey's method in this country.[6] Soon thereafter, enthusiasm for the original Southey tubes seem to have waned, although the procedure is mentioned with high regard in several of the best textbooks of cardiology.[7]

In 1936, there was described a modification of Southey's tubes which deserves much more recognition than it has received. Leech, of Providence, R. I., developed a cannula which in controlled tests drained six times as rapidly as the ordinary Southey tube.[8] It differs from the original in that grooves are milled lengthwise along the tube, leaving four projecting ridges over which the tissues are stretched away from the drainage openings and allowing a constant stream of fluid to enter. We have used the Southey-Leech tube exclusively in recent years, with results considerably superior to those obtained with the ordinary cannula.

The aforementioned substitute method, proposed by McLaren in 1943,[5] employs a series of 18 gage needles instead of a Southey tube. Although this expedient is recommended for use in an emergency in that it uses materials readily available, it cannot be advised for general use. The original report stated that only a liter of fluid was drained in twenty-four hours from the suitable patient on which it was tried; this is considerably less than would be expected with the improved Southey-Leech tube. In our own experience the improvised device has been much less efficient than the Southey-Leech modification.

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4. Southey, R.: Traitement de l'anasarque général par un drainage capillaire, Compt. rend. A. franç. pour l'avancement d. sc. **6**:856, 1877.

5. McLaren, J. A.: An Improvised Southey Tube, Canad. M. A. J. **49**:209 (Sept.) 1943.

6. Bland, E. F., and White, P. D.: The Use of Mechanical Measures in the Treatment of Obstinate Edema, J. A. M. A. **95**:1498 (Nov. 15) 1930.

7. White, P. D.: Heart Disease, ed. 3, New York, The Macmillan Company, 1944, p. 788. Levine, S. A.: Clinical Heart Disease, ed. 3, Philadelphia, W. B. Saunders Company, 1945, p. 281. Lewis, T.: Diseases of the Heart, Described for Practitioners and Students, ed. 4, London, Macmillan & Co., Ltd., 1946, p. 41.

8. Leech, C. B.: An Improvement of Southey's Tubes, J. A. M. A. **106**:1895 (May 30) 1936.

APPARATUS

The improved Southey apparatus was pictured in Leech's original paper.[8] It consists of a trocar and four or six cannulas. It is also necessary to have pieces of rubber tubing to attach to the cannulas. Southey-Leech sets are again available.

PROCEDURE

Although originally described as a method which can be used with the patient reclining in bed, the process is even more effective if the patient is sitting upright, a position which the edematous and orthopneic patient prefers anyway. For best results, he is allowed to sleep all night in a comfortable easy chair. Adequate sedation and plenty of pillows are essential. By morning, the pressure in the tissues of the legs is maximal. A site on the medial or lateral aspect of the lower portion of the leg or of the ankle is usually chosen, although in special circumstances the thighs or scrotum may be used. The legs are cleansed with alcohol, and an antiseptic solution (tincture merthiolate® or nitromersol N.F. [metaphen®]) is applied. When the skin is anesthetized with a drop or two of procaine hydrochloride, the procedure is entirely painless. The Southey-Leech tube, having been previously autoclaved, is mounted on the trocar and thrust deeply into the soft tissues. The cannula is held firmly with a clamp, the trocar is withdrawn and the rubber tubing is attached to drain the fluid into a basin. Two or more tubes are used in each leg. The tubes are usually removed after about eight hours. We have found that the amount of fluid drained in eight or ten hours is ordinarily almost as large as it will be in twenty-four, so we prefer the shorter period. The procedure may be repeated several times, at intervals of a day or two. Crystalline procaine penicillin G, 300,000 units daily, is given as a prophylaxis against local infection, starting the morning before the tubes are inserted and continuing until drainage ceases.

RESULTS

If the patient is a suitable candidate there is a little gush of fluid as soon as the tubes are inserted. A steady trickle continues for many hours. We have seen nearly 22 liters of fluid removed in a single ten hour period. In twenty-four hours the weight has decreased by as much as 27.3 Kg. The drainage has contained as much as 134 Gm. of salt in a single day. Sometimes diuresis is initiated, though the administration of digitalis and mercurial diuretics may previously have been of no avail. Hydrothorax and ascites decrease without thoracentesis or paracentesis. Edema of the forearms disappears without elevating the arms.

During the past six years we have used Southey tubes or the Leech modifications on 62 occasions in 16 patients with refractory or massive edema (table 1). Eleven patients had glomerulonephritis, 2 had heart failure from rheumatic heart disease and 1 from arteriosclerotic heart disease, 1 had generalized lymphosarcomatosis and 1 had constrictive pericarditis. Several, believed to be good candidates for the use of Southey tubes because the edema was soft and pitting, yielded 3 or more liters at a time. Others were thought to be less satisfactory, having edema which was more or less brawny, but Southey tubes were tried

to see what relief might be obtained; usually less than 1 or 2 liters of fluid was removed under these circumstances. Even so, subjective relief was good in most instances and local discomfort was minimal.

TABLE 1.—*Results Obtained by the Use of Southey Tubes in 16 Patients with Massive Edema from Various Causes*

Case	Age	Sex	Diagnosis	Number of Trials	Edema Fluid Lost per Day of Trial, L.	Weight Lost per Day of Trial, Kg.
1	40	F	Nephrotic syndrome	1	21.9	27.2
2	24	M	Nephrotic syndrome	23	1.3-9.4	1.7-12.0
3	32	M	Rheumatic heart disease, congestive heart failure	2	6.6-7.3	7.6+
4	70	M	Diabetes mellitus, arteriosclerotic heart disease, congestive heart failure	3	1.0-2.2	2.9-6.7
5	38	M	Nephrotic syndrome	11	0.2-1.8	0.4-3.0
6	21	M	Nephrotic syndrome	2	2.0-3.7	1.2-3.0
7	27	M	Nephrotic syndrome	5	0.8-4.6	2.5+
8	63	M	Nephrotic syndrome	3	0.6-1.4	2.5-4.6
9	79	M	Lymphosarcomatosis	1	0.5	..
10	25	F	Nephrotic syndrome	1	1.8	2.3
11	17	M	Nephrotic syndrome	2	0.5-1.0	2.5
12	24	F	Nephrotic syndrome	2	1.5-2.5	..
13	73	F	Nephrotic syndrome	1	0.75	..
14	32	M	Nephrotic syndrome	2	1.9-5.4	2.4-6.2
15	36	F	Diabetes mellitus, constrictive pericarditis	2	3.6-5.6	8+
16	42	F	Rheumatic heart disease, congestive heart failure	1	4.0	8.7
			Average of individual measurements		3.0	4.1

TABLE 2.—*Partial Analysis of Edema Fluid Removed with Southey-Leech Tubes on Individual Occasions*

Case	Edema Fluid Removed per Day, L.	Specific Gravity	Protein, Mg./100 Cc.	Chloride, mEq./L.	Chloride Removed per Day (Expressed as Gm. of Sodium Chloride)
1	21.9	1.004	90	105	134
3	7.3	1.006	170	117	49.5
	6.6	1.006	170	102	39.0
4	2.2	1.008	...	112	14.3
	2.0	1.004	510	112	13.0
	1.0	1.003	340	112	6.5
14	5.4	...	...	115	36.4
	1.9	...	...	120	13.4
15	3.6	1.005	150	102	21.4
	5.6	1.005	125	102	33.3

When the whole series is considered, including both likely and unlikely candidates, an average of 3.0 liters of fluid was removed at a time, resulting in an average weight loss of 4.1 Kg. per day. The fluid was characteristically of low specific gravity and of low protein content, with a chloride concentration roughly equivalent to that of serum (table 2). The weight loss was ordinarily somewhat greater than that accounted for by the measured amount of edema fluid, presumably

because of evaporation and unnoticed leakage. The venous pressure of patients with congestive heart failure uniformly fell to normal from initially high levels.

We began using the improved Southey-Leech tube in December 1946, having previously employed the old model. The ordinary Southey tube was used on 22 occasions, removing an average of 1.9 liters of edema fluid per trial. The Southey-Leech tube, employed 40 times, yielded an average of 3.6 liters per trial (table 3). The superiority of the Leech modification was further emphasized by the fact that the patients on whom it was used were on the average somewhat less suitable than those on whom the ordinary tube was tried.

TABLE 3.—*Comparison of Efficiency of the Ordinary Southey Tube and the Improved Southey-Leech Tube in 62 Trials*

	Ordinary Southey Tube	Improved Southey-Leech Tube
Number of trials	22	40
Average amount of edema fluid removed per trial, L.	1.9	3.6

TABLE 4.—*Effect of Prophylactic Administration of Penicillin on the Incidence of Local Infections Following the Use of Southey Tubes*

	Penicillin Not Given	Penicillin Given
Number of trials	41	21
Number of infections	5	0

The efficiency of the Southey-Leech instrument was also compared with that of the substitute device recommended by McLaren,[8] which was used at the same time in an edematous patient. In the left leg there are inserted two Southey-Leech tubes, and in the right leg, three 18 gage needles. In an hour the Southey-Leech tubes had removed 600 cc. of fluid, whereas the improvised device had removed only 120 cc.

No antibiotic drug was given prophylactically during 41 trials, of which 5 (an incidence of 12.2 per cent) were followed by the development of mild cellulitis or thrombophlebitis. All 5 infections occurred in patients with the nephrotic syndrome, which notoriously predisposes to infection and to venous thrombosis.[9] Penicillin was given prophylactically on 21 occasions, following which there were no infections (table 4).

9. Addis, T.: Glomerular Nephritis: Diagnosis and Treatment, New York, The Macmillan Company, 1948, p. 216.

REPORT OF REPRESENTATIVE CASES

CASE 1.—Mrs. V. M., a white American housewife of 40, entered the hospital because of progressive swelling and gain in weight of 60 pounds (27 Kg.) following a severe sore throat about six months previously. She had also noted weakness, blurred vision, nausea and vomiting. Physical examination showed an ill-appearing woman with a blood pressure of 180 systolic and 114 diastolic, retinopathy, hydrothorax, ascites and massive edema. Laboratory studies showed anemia, nitrogen retention, hypoproteinemia, proteinuria and microscopic hematuria. A diagnosis of chronic glomerulonephritis was made. Rest in bed and a low sodium diet gave no relief. In ten hours, Southey-Leech tubes removed 21.9 liters of fluid containing 134 Gm. of chloride (expressed as sodium chloride). The patient lost 27.3 Kg. of weight and felt stronger and less dyspneic.

The loss of nearly 22 liters in a single ten hour trial is an all-time high in our experience. We know of no other therapeutic measure which could approximate this riddance of 22 liters of water, 134 Gm. of salt and 27.3 Kg. of weight in so short a time.

CASE 2.—E. H., a white American electrician of 24, entered 12 times in two years because of recurrent generalized edema. Four years previously he had suffered a severe "streptococcic sore throat." He had been on a low salt diet for several months before his first entry. (Part of the history was reported in more detail elsewhere.[10]) He was an alert, pale young man with hydrothorax, ascites and great swelling of the thoracic wall, the abdomen, the genitalia and the extremities. There was considerable anemia, proteinuria, hypoproteinemia and hypercholesteremia. Nitrogen retention, at first minimal, steadily increased. At intervals of two to four months, Southey-Leech tubes were used for several hours on one or more days, for a total of 23 insertions. Each time there was a rapid loss of weight and a loss of from 1.3 to 9.4 liters of fluid in six to ten hours. Two years after his first entry, the patient died in uremia.

Consistently good relief was afforded during 12 different entries to this hospital extending over twenty-three months, keeping this young man reasonably comfortable during his last two years, which would otherwise have been intolerable.

CASE 3.—D. R., a white American farmer of 32, entered because of edema of six months' duration which was relentlessly progressive despite limitation of activity, a salt-poor diet and the administration of digitalis and diuretics. He had had rheumatic fever at the ages of 4, 10 and 14 years. He was a desperately ill, dyspneic young man, with a blood pressure of 200 systolic and 60 diastolic, signs of both aortic and mitral stenosis and insufficiency, venous distention, hydrothorax, ascites and massive dependent edema. The edema was so severe that he could not be satisfactorily weighed. Rest in bed, a diet containing less than 1 Gm. of salt daily and the administration of digitoxin and mercurial diuretics produced no diuresis or relief during a five day control period. With Southey-Leech tubes, however, 7,300 cc. of edema fluid was removed during the first eight hour trial, and 6,600 cc., two days later. On the latter occasion a 7.6 Kg. loss of

10. Fiese, M. J.: The Use of Southey Tubes in the Treatment of Edema, Stanford M. Bull. 4:45 (May) 1946.

weight was effected. The venous pressure decreased from 15 to 7 cm. of water, and the circulation time (arm to tongue), from thirty-three to twenty seconds.

This patient seemed moribund before Southey-Leech tubes were tried. The underlying heart lesion was obviously irreversible. If evidence was needed of the value of this means of affording comfort, his unbounded gratitude was convincing enough.

CASE 4.—T. W., a white American clerk of 70, entered because of swelling of the ankles for five days. Diabetes mellitus, diagnosed nine years previously, had been controlled with diet alone. Although never before known to have heart disease, the patient had suffered for a week from cough, dyspnea and edema. Physical examination showed an orthopneic little old man with retinal arteriosclerosis, venous distention, hydrothorax, hepatomegaly and dependent edema. Digitoxin in full doses, a diet containing only 1 Gm. of salt daily and the administration of mercurial diuretics brought about almost no change in his weight of 70 Kg. and only a slight increase in the output of urine. After a week of waiting, Southey-Leech tubes were inserted for eight hours on each of three days, allowing a day of rest between trials, with a loss of 2.2, 2.0 and 1.0 liters, respectively. On each day during which the tubes were used the patient's output of urine increased to three or four times its basal level, so that his weight fell to about 56 Kg. in less than a week. The venous pressure fell from 20 to 8 cm. of water, and the circulation time, from thirty-four to twenty-five seconds. The vital capacity increased from 0.7 to 2.4 liters. The symptoms of congestive heart failure were thereafter easily controlled by the administration of digitoxin and the restriction of activity.

Although this patient with arteriosclerotic heart disease was not in desperate straits, the usual therapeutic measures were working slowly. The Southey-Leech tubes drained relatively small amounts—only about 5 liters total in three attempts—but the balance was thereby tipped in his favor, so that diuresis immediately developed and he improved rapidly.

MECHANISM OF ACTION

The physiologic soundness of the use of Southey-Leech tubes has been demonstrated by recent advances in the understanding of edema. Although there are still unanswered questions, one may reasonably postulate a mechanism whereby Southey-Leech tubes are effective. In certain cases of chronic heart failure, according to Warren and Stead, the retention of salt and water in the extracellular compartment precedes and apparently causes hypervolemia and high venous pressure.[11] Without entering into the controversial aspects of the sequence of events in congestive heart failure, it appears that the mechanical removal of fluid reverses this pattern. It has been shown that, other things being equal, the extracellular fluid volume and the plasma volume increase

11. Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure: An Interpretation of the Mechanisms Producing the Edema, Increased Plasma Volume and Elevated Venous Pressure in Certain Patients with Prolonged Congestive Failure, Arch. Int. Med. **73**:138 (Feb.) 1944.

and decrease concordantly.[11] To be precise, the plasma volume is really a part of the extracellular fluid volume. Therefore it would be expected that the rapid removal of large amounts of edema fluid with Southey-Leech tubes would be accompanied with a reduction of the excessive plasma volume, which would in turn be followed by a fall in the venous pressure. Accumulations of extracellular fluid distant from the site of mechanical drainage might then be mobilized, relieving ascites, hydrothorax and edema of the upper part of the body. In a recent exposition of the thesis that retention of fluid is the cause of the picture of congestive heart failure, Starr described the clinical improvement and the lowering of venous pressure following the use of Southey tubes as "the most weighty argument in favor of this view."[12]

Several events in the sequence leading to congestive heart failure are vulnerable to therapeutic attack. Rest may reduce the need for increased cardiac output. The efficiency of the flagging heart may be increased and its cardiac output improved with digitalis. The abnormal resorption of sodium and water by the renal tubule cells may be counteracted with mercurial diuretics. The daily exogenous increment of salt may be minimized with a low sodium diet. Finally, extracellular water and salt may be removed by mechanical means. In mild congestive heart failure attack at a single point may be adequate, i. e., the administration of digitalis may suffice. In severe congestive failure the attack may be directed at several points simultaneously if the situation demands it. Rest, a low sodium diet, the administration of digitalis and diuretics and the mechanical removal of fluid thus supplement one another. Once the excess extracellular water and salt are removed by mechanical means, thereby interrupting the sequence, digitalis and diuretics may, by themselves, be used to maintain cardiac compensation.

In the nephrotic syndrome, the increase of extracellular fluid is not accompanied with corresponding hypervolemia and venous hypertension. The colloid osmotic pressure of the protein-depleted plasma is low, and the blood volume is actually somewhat below normal.[13] The relief following the mechanical removal of edema fluid involves mainly a redistribution of the remaining water and salt within the extracellular compartment. Because the factors previously operative

12. Starr, I.: Our Changing Viewpoint About Congestive Failure, Ann. Int. Med. **30**:1 (Jan.) 1949.

13. Harris, A. W., and Gibson, J. G., II: Clinical Studies of the Blood Volume: VII. Changes in Blood Volume in Bright's Disease With or Without Edema, Renal Insufficiency, or Congestive Heart Failure, and in Hypertension, J. Clin. Investigation **18**:527 (Sept.) 1939. Luetscher, J. A., Jr.: The Effect of a Single Injection of Concentrated Human Serum Albumin on Circulating Proteins and Proteinuria in Nephrosis, ibid. **23**:365 (May) 1944.

are unchanged, deliverance from anasarca may be temporary. This fault is, of course, common to all purely palliative measures. Once excess sodium has been removed, however, the artificial remission can sometimes be prolonged if the dietary intake of salt is restricted.[14] Because the pressure of the extravascular fluid is a factor in maintaining an adequate blood volume in nephrosis,[15] it might be expected that the mechanical removal of edema fluid would lead to serious hypovolemia and shock. Some of our patients demonstrated a slight increase in hematocrit and a slight fall of blood pressure after large amounts of fluid were removed, suggesting that the blood volume was indeed reduced, but the changes were inconstant and were accompanied by no unpleasant symptoms.

As has been noted by others as well, diuresis at times accompanies the removal of fluid with Southey-Leech tubes both in congestive heart failure and in the nephrotic syndrome.[8] Inasmuch as high venous pressure in the kidneys is probably responsible in part for increased resorption of water and salt by the renal tubules,[16] diuresis may, in congestive failure, accompany the reduction of venous pressure that follows the mechanical removal of fluid. Bradley also demonstrated that there is a decrease in the renal excretion of water and sodium when the intra-abdominal pressure is raised, both glomerular filtration and renal blood flow being reduced.[17] Tense accumulations of ascites cause oliguria and retention of salt and water, which may vanish following paracentesis.[18] The relief of ascites often afforded without abdominal paracentesis by the use of Southey-Leech tubes may account for the diuresis which occurs in some cases of the nephrotic syndrome and may be an additional factor in the diuresis of congestive failure.

INDICATIONS AND CONTRAINDICATIONS

The definite indication for the use of Southey-Leech tubes is the presence of any type of massive, soft, pitting edema which has failed to respond to ordinary therapy. The measure is indicated first in

14. Peters, J. P.: The Role of Sodium in the Production of Edema, New England J. Med. **239**:353 (Sept. 2) 1948.

15. Warren, J. V.; Merrill, A. J., and Stead, E. A., Jr.: The Role of the Extracellular Fluid in the Maintenance of a Normal Plasma Volume, J. Clin. Investigation **22**:635 (Sept.) 1943.

16. Bradley, S. E., and Blake, W. D.: Pathogenesis of Renal Dysfunction During Congestive Heart Failure, Am. J. Med. **6**:470 (April) 1949.

17. Bradley, S. E., and Bradley, G. P.: The Effect of Increased Intra-Abdominal Pressure on Renal Function in Man, J. Clin. Investigation **26**:1010 (Sept.) 1947.

18. Thorington, J. M., and Schmidt, C. F.: A Study of Urinary Output and Blood Pressure Changes Resulting in Experimental Ascites, Am. J. M. Sc. **165**:880 (June) 1923.

congestive heart failure from any cause if digitalis, a low sodium diet and diuretics have failed to dispel anasarca, or if immediate relief is imperative. It is indicated in the nephrotic syndrome when low sodium diets and infusions of albumin have failed and when spontaneous diuresis does not occur. There are also certain miscellaneous conditions, such as constrictive pericarditis and chronic hepatitis with portal hypertension, in which the method is useful if other means of treatment have been of no avail.

A relative indication for the use of this method is edema from which rapid relief is desirable, even though the usual therapeutic measures may be expected to be effective. Southey-Leech tubes may be used, for instance, to supplement the administration of digitalis, low sodium diets and diuretics. At times the tubes potentiate these measures or initiate diuresis, the benefit of which can then be continued by routine management.

To recapitulate, Southey-Leech tubes are indicated in two general types of situations: first, to give comfort when all else has failed in such desperate anasarca as that of nephrosis or heart failure, and, second to supplement or potentiate the usual therapeutic measures when rapid alleviation is desirable.

Southey-Leech tubes are contraindicated in any type of edema in which the tissues are infected, brawny or fibrosed, whether the result of heart failure, nephrosis, lymphedema, neoplastic disease, phlebitis or other lesions. Actually, the contraindication is relative, i. e., the softer the edema, the more likely is success, and the harder the edema, the less likely is success. A trial may be warranted in desperate situations even if the prospects for success do not seem good, but the method should not then be condemned if results are minimal.

The use of Southey-Leech tubes has certain advantages over other types of therapy: (1) In ideal cases much time is saved. An amount of fluid is removed in a few hours which if removed at all by routine methods would thereby require days or weeks. (2) The rapid relief afforded by this measure may be the critical factor in the patient's recovery, giving the usual therapeutic methods a better chance of success. (3) Because the method is purely mechanical, the patient's physiologic processes are not disturbed. As the late Thomas Addis pointed out, Southey tubes have been criticized because they leave things fundamentally just as they were before their use; this presumed disadvantage is, however, a point in their favor, for there are methods which do not leave things as they were.[19] For instance, overly vigorous use of mercurial diuretics and low salt diets is sometimes followed by serious

19. Addis,[9] p. 303.

and even fatal depletion of sodium, because salt is lost in proportionately greater amounts than water.[20] Southey tubes, on the other hand, remove electrolytes only in essentially physiologic concentration, thereby avoiding the hazard of sodium depletion.

SUMMARY AND CONCLUSIONS

1. The mechanical removal of edema fluid from the soft tissues, although almost totally neglected in this country, is a valuable and physiologically sound therapeutic procedure.

2. The Leech modification of the Southey tube is superior to the original model and deserves wider recognition than it has received.

3. The prophylactic use of penicillin has abolished the risk of serious infections which in the past sometimes followed the mechanical removal of edema fluid.

4. The definite indication for the use of Southey-Leech tubes is the presence of massive soft pitting edema, whether in the nephrotic syndrome, congestive heart failure or other diseases, which has failed to respond to the usual therapeutic measures.

5. A relative indication for the use of Southey-Leech tubes is the presence of edema from which rapid relief is desirable and in which mechanical methods may supplement and potentiate the therapy ordinarily used.

6. The use of Southey-Leech tubes is contraindicated in infected, hard or brawny edema, in which their use is unsatisfactory and brings unwarranted discredit on the method.

7. Southey-Leech tubes, although rapidly drawing off large amounts of fluid, remove salt in only physiologic concentration, thereby avoiding the serious depletion of sodium which may accompany other methods.

8. Now that the improved Southey-Leech model is available and infection of the puncture sites is no longer a problem, this method of relieving massive edema should be generally revived.

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20. Soloff, L. A., and Zatuchni, J.: Syndrome of Salt Depletion Induced by a Regimen of Sodium Restriction and Sodium Diuresis, J. A. M. A. **139**:1136 (April 23) 1949.

STUDIES ON BONE MARROW IN HYPERGLOBULINEMIA

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THE CLINICAL states in which hyperglobulinemia occurs include the following: multiple myeloma; chronic infections, such as tuberculosis, bronchiectasis and osteomyelitis; lupus erythematosus disseminatus; Boeck's sarcoid; Laennec's cirrhosis; anaphylaxis; carcinomatosis; kala-azar, and a variety of other conditions.[1] Despite the frequency with which hyperglobulinemia occurs, the site of origin of the globulins associated with disease states and, for that matter, of the normal complement of serum globulin is in considerable doubt.[2] Bing,[3] in 1937, summarized the theories of the origin of blood proteins, especially the globulins. Metcoff and Stare[1e] showed that the extrahepatic origin of globulins seemed well established, but that the specific site was still unknown. It is likewise generally accepted that the serum globulins are concerned with the immune mechanisms of the body.[4] The gamma fraction is of chief importance, but the alpha and beta fraction are also

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1. (*a*) Kagan, B. M.: Hyperglobulinemia, Am. J. M. Sc. **206**:309, 1943. (*b*) Jeghers, H., and Selesnick, S.: Hyperproteinemia: Its Significance, Internat. Clin. **3**:248, 1937. (*c*) Gray, S. J., and Barron, E. S. G.: The Electrophoretic Analyses of the Serum Proteins in Diseases of the Liver, J. Clin. Investigation **22**:191, 1943. (*d*) Kolouch, F.; Good, R. A., and Campbell, B.: The Reticulo-Endothelial Origin of the Bone Marrow Plasma Cells in Hypersensitive States, J. Lab. & Clin. Med. **32**:749, 1947. (*e*) Metcoff, J., and Stare, F. J.: The Physiologic and Clinical Significance of Plasma Proteins and Protein Metabolites, New England J. Med. **236**:26, 1947.

2. The upper limit of normal for the total serum globulin is usually stated as 3.0 Gm. per hundred cubic centimeters.[1a,e] In this paper, hyperglobulinemia connotes a level above 3.2 Gm.

3. Bing, J., and Plum, P.: Serum Proteins in Leucopenia, Acta med. Scandinav. **92**:415, 1937.

4. (*a*) Kagan.[1a] (*b*) Metcoff and Stare.[1e] (*c*) Kagan, B. M.: Studies on the Clinical Significance of Serum Proteins: Relationship Between Albumin-Globulin Ratio, Albumen, Globulin and Total Protein, Arch. Int. Med. **71**:157 (Feb.) 1943. (*d*) Kass, E. H.: The Occurrence of Normal Serum Gamma-Globulin in Human Lymphocytes, Science **101**:337, 1945.

believed to play roles in immunity.[5] Presumably, normal globulins and those found in hyperglobulinemic conditions arise from the same sources.[6] Bjørneboe, Gormsen and Lundquist [7] stated that they questioned this assumption. Cannon,[5d] however, pointed out that analyses have shown close chemical similarity.

Sabin [6e] speculated on the origin of antibodies and pointed to the reticuloendothelial system as the most likely site. She used a dye-protein complex which could be followed microscopically through the cells into the serum and demonstrated that the antigen was phagocytosed in cell vacuoles, rendered soluble and then passed into the cytoplasm proper. There the synthesis of globulin was stimulated and some of it modified into antibody globulin. Sabin observed this process in the cells of the reticuloendothelial system (monocytes and macrophages); it was followed by shedding of the surface films and liberation of the antibodies. Cannon [6d] stated that he agreed with this postulate but believed that lymphocytes were also concerned with the production and storage of antibodies. Ehrich and his associates [8] challenged Sabin's concept, stating that the reticuloendothelial system was concerned chiefly, if not solely, with phagocytosis. They stated that they doubted the validity of Sabin's concept of the shedding phenomenon and that there was no evidence to show that the antibodies were products of this process.[8a]

Many observers have favored the theory that serum globulins and antibodies arise in lymphoid tissue. McMaster and Hudack [9] were among the first to show that agglutinins were formed in lymph nodes. Dougherty, Chase and White [10] suggested reticuloendothelial tissue in general and lymphoid tissue in particular as the probable site of antibody production and conceived of the lymphocyte as a storehouse of antibody protein, but not necessarily as its fabricator. Their work demonstrated

5. (*a*) Gray and Barron.[1e] (*b*) Metcoff and Stare.[1e] (*c*) Kass.[4d] (*d*) Cannon, P. R., in Anson, M. L., and Edsall, J. T.: Advances in Protein Chemistry, New York, Academic Press, 1945, vol. 2.

6. (*a*) Metcoff and Stare.[1e] (*b*) Kagan.[4c] (*c*) Kass.[4d] (*d*) Cannon.[5d] (*e*) Sabin, F. R.: Cellular Reactions to a Dye-Protein with a Concept of the Mechanism of Antibody Formation, J. Exper. Med. **70**:67, 1939.

7. Bjørneboe, M.; Gormsen, H., and Lundquist, F.: Further Experimental Studies on the Role of the Plasma Cells as Antibody Producers, J. Immunol. **55**:121, 1947.

8. (*a*) Ehrich, W. E., and Harris, T. N.: The Site of Antibody Formation, Science **101**:28, 1945; (*b*) Ehrich, W. E.: The Functional Significance of the Various Leukocytes in Inflammation, J. Mt. Sinai Hosp. **15**:339, 1949.

9. McMaster, P. D., and Hudack, S. S.: The Formation of Agglutinins Within Lymph Nodes, J. Exper. Med. **61**:783, 1935.

10. Dougherty, T. F.; Chase, J. H., and White, A.: The Demonstration of Antibodies in Lymphocytes, Proc. Soc. Exper. Biol. & Med. **57**:295, 1944.

that gamma globulin was an integral part of the lymphocyte and not simply adsorbed.[10] They suggested that the rate of release of gamma globulin from lymphocytes was under control of the pituitary gland and the adrenal cortex.[11] Ehrich and his associates likewise stated that the lymphocytic theory of antibody formation was established [12] and adduced considerable experimental evidence in its favor. Using the technic of injecting antigen into the foot pad of rabbits, they demonstrated that there was a manifold increase in the antibody titer and in the number of lymphocytes and lymphoblasts in the efferent lymphatics of the popliteal node, and also within the node itself. There was a far greater concentration of antibodies in the cells than in the plasma.[12c] These authors concluded that lymphocytes were instrumental in antibody formation. Whereas they conceded that plasma cells might produce some antibodies, they found no evidence that the cells produce gamma globulin. In similar studies, they concluded that the macrophages and granulocytes were not concerned with antibody formation.[12c] Kass [4d] likewise favored the lymphocytic origin of gamma globulin after experiments similar to those described.

The role of the lymphocyte in antibody production was challenged by Valentine, Craddock and Lawrence.[13] After reviewing the evidence fully, they stated: "It is difficult at the present time to regard as proved that the reported changes in plasma globulins and antibody titers necessarily have resulted from lymphocyte dissolution . . ." [13a] They concluded: "The failure of both massive irradiation and the administration of adrenal cortical hormone to influence the lymph antibody titer in cats suggests that more work is necessary in elucidating the role of lymphoid tissue in the immunologic mechanisms of different species."[13b]

Much has been written on the relationship of plasma cells and hyperglobulinemia. As early as 1913, Hübschmann [14] suggested that plasma

11. Dougherty, T. F.; Chase, J. H., and White, A.: Pituitary-Adrenal Cortical Control of Antibody Release from Lymphocytes, Proc. Soc. Exper. Biol. & Med. **58**:135, 1945.

12. (*a*) Ehrich and Harris.[8a] (*b*) Ehrich, W. E.; Harris, T. N., and Mertens, E.: The Cellular Sources of Antibodies and Other Globulins, Federation Proc. **5**:220, 1946; (*c*) The Absence of Antibody in the Macrophages During Maximum Antibody Formation, J. Exper. Med. **83**:373, 1946.

13. (*a*) Valentine, W. N., Craddock, C. G., and Lawrence, J. S.: Relation of Adrenal Cortical Hormone to Lymphoid Tissue and Lymphocytes, Blood **3**:729, 1948. (*b*) Craddock, C. G.; Valentine, W. N., and Lawrence, J. S.: The Lymphocyte, J. Lab. & Clin. Med. **34**:158, 1949.

14. Hübschmann, P.; cited by Teilum, G.: Allergic Hyperglobulinosis and Hyalinosis (Paramyloidosis) in the Reticulo-Endothelial System in Boeck's Sarcoid and Other Conditions, Am. J. Path. **24**:389, 1948.

cells were able to produce antibodies. Magnus-Levy [15] related the plasma cells in plasma cell myeloma to the hyperglobulinemia characteristic of that disease. Bing and Plum,[3] in 1937, suggested that in various diseases in which hyperglobulinemia is found there is an increase in the bone marrow and elsewhere of plasma cells and other cells belonging to the reticuloendothelial system. They stated that the plasma cell and the reticuloendothelial cell were probably of identical origin and homologous function and concluded that plasma cells were probably precursors of globulins. In later papers, Bing and his co-workers developed and elaborated this concept.[16]

Bing and Neel [16c] vigorously denied that lymphocytes play a part in globulin formation. Bjørneboe and his associates [17] immunized rabbits with polyvalent vaccines and observed massive proliferation of the plasma cells in practically all organs, especially the liver and spleen. The degree of plasma cell proliferation was closely proportional to antibody concentration in the organs and serum. The authors argued against the lymphocyte theory of antibody formation and pointed out that all lymphoid tissue (except perhaps that of the thymus) contains plasma cells. They stated that even a small number of the latter, being an active type of cell, may be of critical importance in the production of antibodies. The same reasoning was used by Ehrich [8b] in a recent publication in which he modified his earlier views on this problem: He argued that there is no hyperglobulinemia in lymphatic leukemia unless there is also proliferation of the plasma cells. Ehrich [8b] and Bjørneboe and his co-workers [7] cited the lack of antibodies in the thymus, an important lymphopoietic organ, in their immunized animals. Ehrich later ascribed a possible but uncertain role to the lymphocyte in the synthesis of antibodies. Fagraeus [18] and Kolouch and his associates [1d] likewise reached the conclusion that the plasma cell is the source of antibodies.

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15. Magnus-Levy, A.: Multiple Myeloma, Acta. med. Scandinav. **95**:217, 1938.

16. (*a*) Bing, J.: Further Investigations in Hyperglobulinemia, Acta med. Scandinav. **103**:547, 1940. (*b*) Bing, J.; Fagraeus, A., and Thorell, B.: Studies on Nucleic Acid Metabolism in Plasma Cells, Acta physiol. Scandinav. **10**:282, 1945. (*c*) Bing, J., and Neel, A. V.: On the Site of Production of Pathologically Increased Globulin as Elucidated by Conditions in the Cerebro-Spinal Fluid, Acta med. Scandinav. **111**:57, 1942. (*d*) Andersen, H. C., and Bing, J.: Further Studies on the Importance of Plasma Cells in the Formation of Globulin, Acta path. et microbiol. Scandinav. **21**:455, 1944.

17. Bjørneboe, Gormsen and Lundquist.[7] Bjørneboe, M.: Serum Proteins During Immunization, Acta path. et microbiol. Scandinav. **20**:221, 1943. Bjørneboe, M., and Gormsen, H.: Experimental Studies on the Role of Plasma Cells as Antibody Producers, ibid. **20**:649, 1943.

18. (*a*) Fagraeus, A.: Plasma Cell Reaction in Antibody Formation. Nord. med. **30**:1381, 1946; (*b*) Plasma Cellular Reaction and Its Relation to the Formation of Antibodies in Vitro, Nature **159**:499, 1947.

Cytochemical methods have recently been brought to bear on the problem of antibody formation. Thorell and Wising [19] showed that the myeloma cell possesses the characteristics of a protein-producing cell, i. e., it has a large nucleolus containing ribose polynucleotides. Bing and his associates [16b] confirmed these observations. More recently various workers,[20] including Ehrich, studied ribose nucleic acid in plasma cells and lymphocytes in artificial immunity states. They found that the lymphocyte loses ribose nucleic acid during maturation but the plasma cell retains it. After injecting typhoid vaccine into the foot pad of rabbits he noted that the curve of production of ribose nucleic acid was similar to the curve of production of antibody. The high concentration of ribose nucleic acid in the cytoplasm of the mature plasma cell suggested that this cell elaborates protein. These authors further demonstrated that the production of antibody and of ribose nucleic acid were associated with the proliferation of plasma cells. They concluded: "These results leave little doubt that also in the lymph node antibody production is accomplished by the plasma cell." [21]

Another method of approaching the problem of the origin of globulins is to study disease states in which globulins are elevated and to consider what light studies on bone marrow may throw on this problem. References in the literature to studies on bone marrow in various specific human diseases (exclusive of multiple myeloma) in which there is hyperglobulinemia are not numerous, nor are the findings consistent. Bing and Plum [3] and Gormsen [22] reported increased plasmacytosis accompanying hyperglobulinemia in leukopenia and agranulocytosis. Markoff [23] and Gormsen [22] reported such an association in serum sickness. Gsell [24] and Gormsen [22] reported plasmacytosis in lymphogranuloma inguinale, but no globulin levels were given. The results in carcinomatosis were inconclusive.[25] In a study of chronic osteomyelitis [26] 6 of 13 patients

19. Thorell, B., and Wising, P. J., cited by Bing, Fagraeus and Thorell.[16b]

20. (*a*) Dougherty, Chase and White.[10] (*b*) Forman, C.; Ehrich, W. E., and Drabkin, D. L.: Nucleic Acids and the Production of Antibody by Plasma Cells, Federation Proc. **8**:355, 1949.

21. Ehrich.[9b] Forman, Ehrich and Drabkin.[20b]

22. Gormsen, H.: Bone Marrow Studies, Copenhagen, Nyt Nordisk Forlag, 1942.

23. Markoff, N. G.: The Reticulo-Endothelial System of the Bone Marrow as Evaluated by Sternal Puncture, Deutches Arch. f. klin. Med. **180**:530, 1937.

24. Gsell, O.: The Significance of the Serum Protein and Bone Marrow Changes in Lymphogranuloma Inguinale, Klin. Wchnschr. **18**:778, 1939.

25. Gormsen.[22] Delcourt, R.: Concerning the Plasmacytic Marrow Reaction in Cancerous Patients, Sang **17**:202, 1946.

26. Carboncini, G., and Altana, G.: The Hyperplastic Reaction of the Bone Marrow Reticulum in the Course of Chronic Osteomyelitis, Hematologica **28**:293, 1946.

with serum globulin levels over 3.0 Gm. per cubic centimeter had increased plasma cells in the bone marrow. In these cases there was no correlation between the levels for plasma cells and for serum globulin. Söderhjelm [27] reported 22 cases, mostly of chronic infection, with hyperglobulinemia. In his series, an increased plasma cell content was found in 7 cases. Most and Lavietes [28] reported that in 7 cases of kala-azar in which studies on bone marrow were done and in all of which there was hyperglobulinemia the differential counts on the marrow were normal. In a recent study of 8 cases of hyperglobulinemia with various etiologic factors an increased number of plasma cells in the bone marrow was noted in 3.[29] In a report of studies on bone marrow, Gormsen [22] stated that the correlation between serum globulins and plasma cells, while real, does not exist in all cases. He added, however, that when there were more than 5 per cent plasma cells there was always hyperglobulinemia.

Of considerable interest is a recent report of studies of the peripheral blood and the bone marrow in patients with chronic hepatic insufficiency by Jarrold and Vilter.[30] In 30 cases of proved Laennec's cirrhosis the average amount of plasma cells in the bone marrow was 10.5 per cent (expressed as percentage of nonerythroid nucleated cells) and in these the plasmacytosis was approximately proportional to the degree of hyperglobulinemia. Lymphocytes in the bone marrow were at the upper limits of normal, and there was a distinct tendency toward eosinophilia (not mentioned by the authors, but evident from their data). On the other hand, these workers did not find significant plasmacytosis of the marrow in 7 cases each of infectious hepatitis and biliary cirrhosis.

MATERIALS AND METHODS

The present study was undertaken to determine whether any correlation existed between the hyperglobulinemia in the serum and the number of plasma cells in the bone marrow, as suggested in experimental immune states in rabbits.[7] We studied 33 patients with serum globulin levels of 3.2 Gm. or more per hundred cubic centimeters. In 11 cases the diagnosis was rheumatoid arthritis, in 6 there was cirrhosis of the liver and in the remainder there were a miscellany of disorders. Twenty of our cases showed clinical evidence of chronic infection. In 26 cases the hyperglobulinemia was confirmed by a positive reaction in the formol-gel test,

27. Söderhjelm, A. L.: Plasma Cells in the Bone Marrow in Cases of Hyperglobulinemia, Nord. med. **33**:24, 1947.

28. Most, H., and Lavietes, P. H.: Kala-Azar in American Military Personnel, Medicine **26**:221, 1947.

29. Rowen, M. J.: Personal communication to the authors.

30. Jarrold, T., and Vilter, R. W.: Hematologic Observations in Patients with Chronic Hepatic Insufficiency, J. Clin. Investigation **28**:286, 1949.

performed according to the technic of Wise and Gutman.[31] The serum globulin level was 4.0 Gm. or more per hundred cubic centimeters in each of the 7 cases in which the test was not made.

The peripheral leukocyte and differential counts recorded were representative of nonfebrile states. Aspirations of the bone marrow were obtained either from the sternum or from the iliac crest. The uncentrifuged aspirate was smeared, and a differential count of the nucleated cells was done. In the majority of instances 500 nucleated cells were counted by each of two of us (I. B. and S. L. W); there was excellent agreement in every case. The figures in table 1 give, for each cell type, the percentage of total nucleated cells.

TABLE 1.—*Bone Marrow Findings in Patients with Hyperglobulinemia*

Patient	Neutrophils, %				Eosinophils	Basophils	Lymphocytes	Plasma Cells	Monocytes	Reticuloendothelial Cells	Megaloblasts	Erythroblasts	Normoblasts	Undifferentiated Cells
	Myeloblasts	Myelocytes	Nonsegmented Cells	Segmented Cells										
1	0.7	16.2	17.6	19.1	6.0	0.6	15.2	1.9	1.2	0.3	0.7	1.9	18.5	0.1
2	0.4	9.6	17.7	22.3	4.7	0.0	30.0	0.6	0.6	0.1	0.5	2.0	11.5	0.0
3	0.0	11.3	25.2	11.5	4.4	0.3	15.5	0.6	1.9	0.0	0.7	3.8	24.5	0.3
4	0.5	18.7	28.3	8.5	9.2	0.6	8.5	0.6	1.2	0.7	0.5	1.2	21.5	0.0
5	2.4	14.1	18.2	27.8	2.4	0.1	15.1	0.4	2.2	0.2	0.6	2.0	14.5	0.0
6	1.4	16.1	24.1	15.4	3.0	0.6	5.5	1.7	0.4	0.7	2.1	6.4	22.0	0.5
7	0.0	16.5	31.4	17.1	3.0	0.3	5.4	1.4	0.8	0.1	1.0	1.6	21.4	0.0
8	0.0	19.2	47.0	7.8	1.3	0.2	2.5	3.0	2.4	0.4	0.7	0.8	14.5	0.2
9	0.5	11.1	13.9	19.0	4.1	0.1	28.1	0.6	1.6	0.1	0.2	0.8	19.7	0.2
10	1.1	11.3	18.9	17.0	1.1	0.1	17.3	2.6	0.8	0.4	0.4	1.1	27.6	0.3
11	0.0	22.0	16.4	15.5	2.6	0.0	9.0	1.2	0.3	0.0	0.0	2.2	30.8	0.0
12	1.6	22.8	20.2	15.8	2.4	0.4	18.5	0.6	1.0	0.6	0.0	0.6	15.2	0.3
13	0.3	15.7	25.9	23.6	2.1	0.1	6.4	1.2	0.0	0.3	0.0	2.8	21.6	0.0
14	0.0	19.4	30.7	19.9	2.0	0.0	8.7	0.4	0.0	0.0	0.0	0.5	18.4	0.0
15	0.0	7.2	22.3	31.2	7.6	0.5	11.6	0.6	1.2	0.4	0.2	1.0	16.1	0.1
16	0.0	17.2	19.3	18.0	3.3	0.0	26.4	0.3	0.0	0.0	0.0	0.6	14.9	0.0
17	0.2	25.4	26.2	25.7	1.7	0.0	11.0	1.7	0.4	0.0	0.6	2.6	4.4	0.1
18	0.0	13.6	21.3	6.7	1.2	0.0	2.4	0.5	0.3	4.2	1.1	3.2	45.5	0.0
19	1.8	17.2	33.6	13.4	2.7	0.0	10.6	0.7	0.3	0.1	0.6	1.4	17.6	0.0
20	0.4	18.3	17.5	31.8	2.3	0.0	11.3	5.5	0.0	0.0	0.0	0.9	12.0	0.0
21	2.2	14.5	16.4	18.9	5.7	0.6	10.3	2.5	0.8	0.3	0.2	2.4	24.4	0.8
22	0.0	20.8	29.6	24.8	1.3	0.0	9.0	0.0	0.0	0.0	0.1	5.1	9.3	0.0
23	3.3	19.7	18.8	25.0	3.2	0.0	15.0	1.0	0.0	0.0	0.4	1.0	11.0	0.0
24	0.2	14.4	13.6	26.0	1.0	0.0	22.2	1.7	0.0	0.0	0.3	0.3	20.2	0.0
25	0.3	19.1	20.2	26.3	6.2	0.2	6.5	1.5	1.1	0.6	0.0	1.6	25.3	0.1
26	1.1	15.6	21.8	14.8	1.5	0.1	4.8	1.0	0.3	0.4	2.4	4.1	31.9	0.2
27	0.3	10.0	24.2	23.9	12.5	0.0	19.0	1.2	0.6	0.5	0.0	0.3	7.4	0.1
28	0.2	19.8	20.5	11.5	2.4	0.4	16.4	1.0	0.3	0.0	0.7	1.2	25.5	0.1
29	0.4	6.2	17.1	27.3	2.3	0.1	7.2	4.9	0.7	0.2	1.4	5.7	26.4	0.0
30	1.3	9.5	24.5	16.5	12.7	0.4	12.0	0.5	1.7	0.2	0.1	0.4	20.0	0.2
31	0.5	14.2	28.8	10.3	2.3	0.1	10.4	1.1	0.8	0.0	0.5	1.4	29.5	0.1
32	0.0	10.0	25.3	17.3	12.4	0.0	8.0	0.5	2.6	0.0	0.2	6.6	17.1	0.0
33	0.0	12.8	10.1	21.8	0.1	0.0	39.0	1.4	0.0	0.0	0.2	0.6	14.0	0.0

Serum albumin and globulin determinations were made by the Tuchman and Sobotka modification of the Folin and Ciocalteu method.[32] Electrophoretic analyses of the serum of 4 patients were done.[33] Results of these are shown in table 2.

31. Wise, C. R., and Gutman, A. B.: Formol Gel Reaction, Am. J. M. Sc. **194**:263, 1937.

32. Tuchman, L. R., and Sobotka, H.: Comparison of Wu and Kjeldahl Methods of Serum Protein Determinations, J. Biol. Chem. **98**:35, 1932. Protein values were determined in the clinical laboratory, Dr. J. Rosenthal, Director.

33. Electrophoretic analyses of the serum were done through the courtesy of Dr. Dan H. Moore, Department of Biochemistry, Columbia University College of Physicians and Surgeons.

Cephalin flocculation tests [34] were performed in 31 cases and thymol turbidity tests [35] in 24. Sulfobromophthalein tests were performed in 20 cases, and prothrombin time [36] was determined in 25.

RESULTS

Table 3 lists the patients in order of increasing serum globulin levels. Leukocyte counts on the peripheral blood, lymphocyte percentages and results of the tests for cephalin flocculation and thymol turbidity and of the sulfobromophthalein test are included; prothrombin time is given. There was no correlation between serum globulin levels and either total leukocyte counts on the peripheral blood or lymphocyte percentages. No plasma cells were seen in any of the peripheral blood smears. Twenty of the patients had moderate to severe anemia consistent with their chief illnesses. Seven had eosinophilia of 8 to 17 per cent. The reaction to the cephalin flocculation test was greater than 2 plus in 20 of 30 cases; the value for the thymol turbidity test was abnormal (over 4.0

TABLE 2.—*Electrophoretic Analyses in 4 Patients with Hyperglobulinemia*

Patient	Plasma Cells in Bone Marrow, %	Serum Albumin, Gm./100 Cc.	Serum Globulin, Gm./100 Cc.		
			Alpha	Beta	Gamma
6	1.7	3.55	0.58	1.60	2.20
11	1.2	4.00	0.50	1.15	1.65
21	2.5	3.93	0.92	1.45	3.00
27	1.2	2.85	1.40	1.50	3.80

units) in 20 of 23. There was abnormal dye retention in the sulfobromophthalein test in 11 cases, and an elevated prothrombin time, in 15.

Table 1 gives the differential counts on the bone marrow in 33 cases. There was no bone marrow picture characteristic of hyperglobulinemia. Plasma cells normally appear in the bone marrow in quantities of between 1.8 and 3.0 per cent of total nucleated cells.[37] We selected the lower of these values as the upper limit of normal. Only 6 patients had plasma cell levels of 1.8 per cent or greater, and the highest of

34. Hanger, F. M.: Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, J. Clin. Investigation **18**:261, 1939.

35. Shank, R. E., and Hoagland, C. L.: Modified Method for Quantitative Determination of Thymol Turbidity Reaction of Serum, J. Biol. Chem. **162**:133, 1946.

36. Shapiro, S.; Sherwin, B.; Redish, M., and Campbell, H. A.: Prothrombin Estimation: Procedure and Clinical Interpretations, Proc. Soc. Exper. Biol. & Med. **50**:85, 1942. Prothrombin times were determined in the laboratory of Dr. Shepard Shapiro.

37. Gormsen.[22] Osgood, E. E., and Seaman, A. J.: The Cellular Composition of Normal Bone Marrow as Obtained by Sternal Puncture, Physiol. Rev. **24**:46, 1944.

TABLE 3.—*Studies of Peripheral Blood and Hepatic Function in Patients with Hyperglobulinemia*

Patient	Age, Years	Sex	Diagnosis	Peripheral Blood: Serum Protein, Gm./100 Cc. Albumin	Peripheral Blood: Serum Protein, Gm./100 Cc. Globulin	Peripheral Blood: Lymphocytes, W. B. C./Cu. Mm.	Peripheral Blood: Lymphocytes, Percentage	Peripheral Blood: Other Abnormalities	Hepatic Function: Cephalin Flocculation	Hepatic Function: Thymol Turbidity Units	Hepatic Function: Dye Retention, Sulfobromophthalein Test, %	Hepatic Function: Dye Retention, Sulfobromophthalein Test, Min.	Hepatic Function: Prothrombin Time, Seconds, Whole	Hepatic Function: Prothrombin Time, Seconds, Dilute*
1	51	F	Rheumatoid arthritis	3.5	3.2	8,000	20	8% eosinophilia	4+	11.7	..	..	18.5	54.2
2	62	F	Rheumatoid arthritis	3.3	3.2	8,500	24	None	3+	8.6	20	30	16.5	40.5
3	71	M	Rheumatoid arthritis	4.3	3.3	7,800	30	Moderate anemia	4+	10.0	..	..	19.9	38.7
4	56	M	Rheumatoid arthritis; amyloidosis	3.2	3.2	10,000	25	8% eosinophilia; severe anemia	1+	....	5	30	....	....
5	55	M	Rheumatoid arthritis; rheumatic heart disease	4.3	3.3	12,000	18	None	0	3.1	0	30	20.2	46.0
6	66	F	Rheumatoid arthritis; lipid pneumonia	4.4	3.6	7,000	3.5	None	3+	5.8	..	..	23.5	60.0
7	73	M	Rheumatoid arthritis	3.8	3.6	8,200	31	None	0	11.3	7	30	19.5	32.0
8	61	M	Rheumatic heart disease; subacute bacterial endocarditis	3.8	3.6	9,000	43	Severe anemia	4+	25.0	0	30	24.3	42.5
9	48	F	Rheumatoid arthritis	4.5	3.6	7,200	26.5	9% eosinophilia; moderate anemia	4+	25.3	5	45	19.3	44.8
10	75	M	Cirrhosis of liver; syphilitic periostitis	3.2	3.6	7,100	25	None	4+	8.3	35	45	....	....
11	69	M	Postpneumonic pulmonary fibrosis	4.3	3.7	7,000	22	Moderate anemia	4+	2.4	15	45	21.1	49.2
12	58	F	Rheumatoid arthritis; rheumatic heart disease	3.2	3.7	4,500	50	Moderate anemia	4+	13.3	..	..	19.0	39.3
13	56	M	Cirrhosis of liver	3.0	3.7	8,500	27	Moderate anemia	4+	8.3	30	45	23.0	60.0
14	70	M	Rheumatoid arthritis	3.7	3.7	10,800	23	Moderate anemia	....	....	..	..	....	....
15	54	M	Xanthomatous biliary cirrhosis	4.0	3.8	11,900	22	Moderate anemia	1+	8.4	..	..	....	....
16	23	F	Transverse myelitis; chronic osteomyelitis; chronic pyelonephritis	4.2	3.8	12,500	24	Severe anemia	0	10.1	..	..	20.0	48.1
17	38	M	Rheumatoid arthritis; amyloidosis	3.7	4.0	9,600	26	Severe anemia	2+	11.8	44	30	25.5	43.7
18	51	M	Cirrhosis of liver	3.7	4.1	3,500	20	None	4+	4.0	10	45	18.7	61.8
19	53	M	Bronchogenic carcinoma with metastases	4.2	4.1	18,000	24	Moderate anemia	....	....	..	..	....	....
20	24	F	Disseminated disease of collagen, type undetermined	2.9	4.1	4,500	15	Moderate anemia	4+	....	0	30	....	....
21	74	F	Bronchiectasis	3.7	4.2	7,500	25	14% eosinophilia	1+	6.0	..	..	24.0	31.1
22	55	M	Syphilitic heart disease; subacute bacterial endocarditis	3.2	4.2	8,000	24	Moderate anemia	2+	....	5	30	16.8	41.4
23	27	F	Disseminated lupus erythematosis	3.0	4.4	6,600	38	Severe anemia	3+	....	3	30	14.5	38.6
24	62	F	Pseudohemophilia	2.5	4.5	10,000	18	Severe anemia	0	....	0	30	18.5	45.2
25	96	F	Infected varicose ulcers of leg; latent syphilis	3.7	4.6	11,000	26	Moderate anemia	4+	4.1	50	45	23.3	52.5
26	81	F	Chronic cholecystitis; diabetes mellitus	3.7	4.7	6,000	46	None	0	8.3	..	..	....	....
27	47	M	Chronic erythroderma with melanosis	3.7	5.2	16,000	34	8% eosinophilia	0	4.5	5	30	21.0	32.6
28	75	M	Cirrhosis of liver	2.2	5.4	7,400	50	None	1+	4.7	20	30	24.0	75.0
29	72	M	Chronic pancreatitis and cholecystitis	3.0	5.6	10,350	10	None	4+	7.6	20	30	24.6	48.0
30	56	M	Hodgkin's disease; cirrhosis of liver	3.6	5.7	8,000	25	17% eosinophilia	3+	....	20	30	15.1	28.5
31	40	M	Cirrhosis of liver	2.1	5.9	5,100	36	Moderate anemia	3+	17.4	..	..	26.0	60.0
32	43	F	Nonspecific granulomatosis	2.9	6.0	6,200	33	14% eosinophilia; moderate anemia	3+	....	..	..	20.8	50.0
33	52	F	Severe anemia, cause unknown	4.1	7.8	3,000	28	Severe anemia	3+	10.0	..	..	....	....

* Dilute prothrombin times were determined with a 12.5 per cent solution of plasma.[26]

these was 5.5 per cent. The lymphocyte counts varied from 2.5 per cent to 39.0 per cent. Eleven patients, including all 7 with peripheral eosinophilia, had more than 4 per cent eosinophils in the bone marrow. Table 4 demonstrates, however, that the number of plasma cells, lymphocytes and eosinophils in the bone marrow was not related with any constancy to the serum globulin levels.

TABLE 4.—*Comparison of Plasma Cells, Lymphocytes and Eosinophils in Bone Marrow with Serum Globulin Levels*

Patient	Serum Globulin, Gm./100 Cc.	Bone Marrow		
		Plasma Cells, %	Lymphocytes, %	Eosinophils, %
1	3.2	1.9	15.2	6.0
2	3.2	0.6	30.0	4.7
3	3.2	0.6	15.5	4.4
4	3.2	0.6	8.5	9.2
5	3.3	0.4	15.1	2.4
Average		0.8	16.9	5.3
6	3.6	1.7	5.5	3.0
7	3.6	1.4	5.4	3.0
8	3.6	3.0	2.5	1.3
9	3.6	0.6	28.1	4.1
10	3.6	2.6	17.3	1.1
Average		1.9	11.8	2.5
11	3.7	1.2	9.0	2.6
12	3.7	0.6	18.5	2.4
13	3.7	1.2	6.4	2.1
14	3.7	0.4	8.7	2.0
15	3.8	0.6	11.6	7.6
16	3.8	0.3	26.4	3.3
Average		0.7	13.4	3.3
17	4.0	1.7	11.0	1.7
18	4.1	0.5	2.4	1.2
19	4.1	0.7	19.6	2.7
20	4.1	5.5	11.3	2.3
21	4.2	2.5	10.3	5.7
22	4.2	0.0	9.0	1.3
Average		1.8	9.1	2.5
23	4.4	1.0	15.0	3.2
24	4.5	1.7	22.3	1.0
25	4.6	1.5	6.5	6.2
26	4.7	1.0	4.8	1.5
Average		1.3	12.2	3.0
27	5.2	1.3	19.0	12.5
28	5.4	1.0	16.4	2.4
29	5.6	4.9	7.3	2.3
30	5.7	0.5	12.0	12.7
31	5.9	1.1	10.4	2.3
32	6.0	0.5	8.0	12.4
33	7.8	1.4	39.0	0.1
Average		1.5	16.0	6.4

There was no relationship between the gamma globulin levels of the serum as estimated by electrophoresis and the number of plasma cells in the bone marrow (table 2) in the 4 cases in which these examinations were made.

COMMENT

It is evident that there is great confusion concerning the origin of serum globulins and antibodies. Many theories have been proposed. The two most prevalent concepts at the time of this report are those of the lymphoid and plasma cell origins of globulins. More or less valid objections to each have been raised by various authors. Among

the chief objections to the lymphoid theory are the lack of proof that reported changes in plasma globulins and antibody titers have necessarily resulted from the dissolution of lymphocytes,[13a] the absence of hyperglobulinemia in the majority of cases of chronic lymphatic leukemia and the lack of antibodies in the thymus.[38] Recent work on ribose nucleic acid metabolism tends to show that lymphocytes are not protein-producing cells.[39]

To the plasma cell theory of globulin formation may be brought an imposing array of experimental support. In experimentally produced immunity states, the proliferation of plasma cells has been noted in the spleen, the liver, the bone marrow and the renal sinuses.[40] Cytochemical studies have shown that the plasma cell, in contrast to the lymphocyte, is a protein-producing cell.[8b] In addition, some clinical studies have demonstrated a correlation between hyperglobulinemia and plasmacytosis in the marrow. On the other hand, although a frequent association of the two has been observed this relationship is inconstant, and even in multiple myeloma there is frequently no correlation.[41] We have shown that in the relatively few reports of studies on bone marrow in hyperglobulinemia the results are inconsistent and, taken in the aggregate, do not support the theory of the origin of globulins in the plasma cells of the bone marrow.

Several other possibilities exist to explain the diverse results reported. It has been proposed that plasmacytosis and hyperglobulinemia may coexist as a result of a common stimulus.[42] Waldenström [43] advanced the concept that the hyperglobulinemia may be the primary disorder and the plasmacytosis secondary to it, perhaps being a means of storage. This concept was disputed by Ranström.[42] Where hyperglobulinemia exists without plasmacytosis in the bone marrow, other sites of proliferation of plasma cells must be considered, especially the liver and spleen or the specific sites of chronic infection. It is also conceivable that globulins are formed at several different sources, namely, in plasma cells, lymphocytes and reticuloendothelial cells.[44]

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38. Bjørneboe, Gormsen and Lundquist.[7] Ehrich.[8b]

39. Ehrich.[8b] Forman, Ehrich and Drabkin.[20b]

40. Kolouch, Good and Campbell.[1d] Bjørneboe, Gormsen and Lundquist.[7] Fagraeus.[18a]

41. Diggs, L. W., and Sirridge, M. S.: A Study of the Sternal Marrow and Peripheral Blood of Fifty-Five Patients with Plasma Cell Myeloma, J. Lab. & Clin. Med. **32**:167, 1947.

42. Ranström, S.: On the Terms "Essential Hyperglobulinemia" and "Premyeloma," Acta med. Scandinav. **124**:134, 1946.

43. Waldenström, J.: On the Terms "Essential Hyperglobulinemia" and "Premyeloma," Acta med. Scandinav. **124**:148, 1946.

44. Bjørneboe, Gormsen and Lundquist.[7] Ehrich.[8b] Jarrold and Vilter.[30] Waldenström.[43]

Our study showed no consistent findings in the bone marrow in hyperglobulinemia. There was no correlation whatever among serum globulin levels, the amount of lymphocytes in the peripheral blood or in the bone marrow and plasmacytosis in the bone marrow. The group of patients with the highest globulins showed, as an average, a normal plasma cell count.

Our series included 6 cases of Laennec's cirrhosis, in only 1 of which there was an increased number of plasma cells in the marrow. This was in contrast to the findings of Jarrold and Vilter.[30] A striking number of abnormal results of hepatic function tests was recorded in our patients in whom manifest clinical hepatic insufficiency was not demonstrable. The results of the cephalin flocculation and thymol turbidity tests may be ascribed to the presence of abnormal globulins.[10] The results of the sulfobromophthalein tests and the prothrombin studies are not so easily explained. The relationship of hepatic disease, hyperglobulinemia and changes in the bone marrow is under investigation.

Electrophoretic studies of the serum in 4 cases showed no correlation between the elevated gamma globulin level and the number of plasma cells in the bone marrow.

We are unable to explain the significance of eosinophilia of the marrow in our cases and in those of Jarrold and Vilter.[30] There was no relation between the level of the serum globulin and the percentage of eosinophils.

SUMMARY

1. Of 33 persons with hyperglobulinemia elevation of the plasma cells in the bone marrow occurred in 6.

2. There was no correlation between the levels of serum globulin and of plasma cells in the bone marrow.

3. Elevated serum globulin in 4 cases was mainly in the gamma globulin fraction and was not related to the number of plasma cells in the bone marrow.

4. No significant changes were noted in the levels of lymphocytes in the bone marrow.

5. Eosinophils in the bone marrow were elevated in one third of the patients.

Progress in Internal Medicine

INFECTIOUS DISEASES

Fifteenth Annual Review of Significant Publications

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FOR THE fifth successive year statistics indicate an uninterrupted decline in the mortality rate for infectious diseases. Records of a large life insurance company [1] establish an "all time low" mortality rate for 1948 and a "record-breaking low" for the first six months of 1949. There has been a drop of 22 per cent in the death rate from tuberculosis in two years. Scarlet fever, diphtheria, whooping cough, syphilis, enteritis, pneumonia and influenza have the lowest death rates ever recorded. That for pneumonia is 40 per cent below the average for the ten year period of 1938 through 1947. Much of the decline in mortality from the diseases mentioned is due to the successful specific therapy or prophylaxis now available. On the other hand, the number of cases of poliomyelitis was exceeded only once before, in 1916. This increase may be due partly to better diagnosis and to better reporting of cases.

At the time of writing four important diseases, among others, resist attempts at specific therapy; in three of these the exact cause is still unknown. They are poliomyelitis, the minor infections of the respiratory tract, viral hepatitis and acute rheumatic fever. Even rheumatic heart disease is said to have shown a 90 per cent drop in mortality rate since 1920, 85 per cent in the last seven years as a result of the control of infections which lead to rheumatic fever.[2]

Probably the most important developments in the past year were the success of aureomycin and chloramphenicol (chloromycetin®) in the treatment of a number of infections and the evidence that rheumatoid arthritis may not be an infectious disease.

In last year's review,[3] mention was made of the surprisingly few instances reported of exotic diseases in veterans who had returned from endemic areas after the war. However, there is reason to believe the number of instances actually to be greater than has been reported. Many

From the Jefferson Medical College and Hospital.

1. Mortality at All-Time Low in 1948, Statist. Bull. Metrop. Life Insur. Co. **30**:1-5 (Jan.) 1949; Record-Breaking Low Mortality in 1949, ibid. **30**:3-5 (July) 1949.

2. Rheumatic Fever Mortality Rate Declining, Medical News, J. A. M. A. **139**:469 (Feb. 12) 1949.

3. Reimann, H. A.: Infectious Diseases, Arch. Int. Med. **82**:468 (Nov.) 1948.

cases, no doubt, are unrecognized because of the unfamiliarity of physicians with the group of diseases in question, and laboratories are seldom equipped for their detection. Moreover, many veterans with "tropical" or parasitic infections are regarded as psychoneurotic. Of nearly 500 veterans examined in Mackie's clinic,[4] 64 per cent carried intestinal helminths or protozoa, 39 per cent of which were Endamoeba histolytica. A correct diagnosis almost invariably had not been made previously. On the other hand, the incidence of relapsing malaria is rapidly decreasing and no serious sequelae of filariasis or schistosomiasis were seen.

ANTIBIOTIC AGENTS

The intensive search for new antibiotics has discovered several more of value and others of probable value. So many are now at hand that one may almost predict the rise of a new specialist, the antibioticist, who would determine which antibiotic to use for what disease and how.

Penicillin.—It has been the general opinion that, fortunately, except for staphylococci and streptococci of the viridans group, few bacteria become resistant to penicillin during therapy. Hirsch and his co-workers [5] stated that in 14 of 75 patients bacteremia recurred during therapy and in each patient increased resistance of the cocci to penicillin was demonstrated. Most of the infections were caused by staphylococci, 3 by viridans and 1 by hemolytic streptococci. Miller and Bohnhoff [6] increased the resistance of a type 1 strain of meningococci one hundred and seventy fold by passage in mice treated with small doses of penicillin. This resistance developed in vivo and was lost on passage on an artificial medium, but the cocci retained their virulence throughout. As an opposite effect, Plough and Grimm,[7] studying a penicillin-resistant strain of Salmonella typhimurium (a gram-negative bacillus), isolated a variant therefrom which was sensitive to penicillin.

Use in Pneumococcic Pneumonia: Price [8] treated patients with pneumococcic pneumonia successfully with injections of 100,000 units

4. Mackie, T. T., and Sonnenberg, B.: Tropical Disease Problems Among Veterans of World War II, Am. J. Trop. Med. **29**:443-451 (July) 1949.

5. Hirsch, H. L.; Dowling, H. F., and Robinson, J. A.: Organisms Resistant to Penicillin Obtained from Patients, Arch. Int. Med. **82**:310-318 (Sept.) 1948.

6. Miller, C. P., and Bohnhoff, M.: Studies on the Action of Penicillin: VII. Development of Penicillin Resistance by Meningococcus in Vivo, J. Infect. Dis. **83**:256-261 (Nov.-Dec.) 1948.

7. Plough, H. H., and Grimm, M. R.: Reversal to Penicillin Sensitivity in a Cysteine-Requiring Mutant of Salmonella, Science **109**:173-174 (Feb. 18) 1949.

8. Price, A. H.: Aqueous Penicillin Therapy for Pneumococcic Pneumonia: Injections at Twelve Hour Intervals, J. A. M. A. **138**:292-293 (Sept. 25) 1948.

of penicillin in aqueous solution, given intramuscularly every twelve hours. Subsequently other authors reported similar good effects. In one series 300,000 units once daily sufficed.[9] Volini and his group[10] treated patients orally by giving 200,000 units at once and 100,000 units every three hours, for an average dosage of 4,400,000 units over an average period of 5.8 days. The mortality rate among 48 patients was 6.3 per cent. Oral therapy, the authors state, is superior to therapy with sulfonamide compounds and almost equal in value to the parenteral administration of penicillin. The chief objection is the cost. Purulent complications require local and parenteral treatment.

Superinfection with both Escherichia coli and Aerobacter aerogenes developed during penicillin therapy in 2 patients with type II pneumococcic pneumonia. Administration of streptomycin controlled the secondary infections promptly. Because of the rarity of such superinfection there is no justification for routinely combining penicillin and streptomycin, but it is necessary to anticipate the possibility of such occurrences.[11]

Use in Other Diseases: Dowling and his co-workers[12] recommend the intramuscular injection of 1,000,000 units of penicillin every two hours, or 12,000,000 units a day, for the treatment of pneumococcic meningitis. The mortality rate with this dosage was 38 per cent. Since the figure is not significantly lower than that in a number of other cases in which much smaller doses were used, the amount recommended seems excessive. Intrathecal injection is not advised.

Archer and his associates[13] point out how therapy with penicillin may modify and obscure the course of disease. They report an instance in which successful treatment of diverticulitis delayed recognition of carcinoma of the colon. Penicillin may so modify the course of osteomyelitis, pulmonary abscess, perinephritic abscess, mastoiditis, cholecystitis and other infections that serious structural damage may progress unnoticed unless careful observations are made.

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9. Weiss, W., and Steinberg, I.: Treatment of Pneumonia with Intramuscular Penicillin Once a Day, Am. J. M. Sc. **217**:86-91 (Jan.) 1949.

10. Volini, I. F.; Hoffman, W.; Hughes, J. R., and Peffer, J. R.: Studies in the Oral Administration of Penicillin: III. Oral Penicillin in the Treatment of Pneumococcic Pneumonia, Illinois M. J. **94**:235-241 (Oct.) 1948.

11. Applebaum, E., and Leff, W. A.: Occurrence of Superinfection During Antibiotic Therapy, J. A. M. A. **138**:119-121 (Sept. 11) 1948.

12. Dowling, H. F.; Sweet, L. K.; Robinson, J. A.; Zellers, W. W., and Hirsch, H. L.: Treatment of Pneumococcic Meningitis with Massive Doses of Systemic Penicillin, Am. J. M. Sc. **217**:149-156 (Feb.) 1949.

13. Archer, V. W.; Cooper, G., Jr., and Adair, N.: Symptoms Masked or Modified by Chemotherapy: Increasing Responsibility of Roentgenologist, J. A. M. A. **138**:645-650 (Oct. 30) 1948.

Among others, Wilson and his co-workers [14] point out the dangers of injecting serums, drugs and antibiotics into the spinal canal. Even a diagnostic spinal puncture may cause irritation, pleocytosis and symptoms. The authors report a number of serious neurologic reactions after the intrathecal injection of various agents, including penicillin, and conclude that this mode of therapy is ". . . truly meddlesome mischief and is strictly contraindicated." It is illogical especially when other routes of administration are satisfactory and dangerous when there is any abnormality of the nervous system. The view held by Price, Hoyne [15] and me that intrathecal antibiotic therapy is unnecessary is also supported in experimental studies.[16] In cats, even when meningitis was caused by intrathecal inoculation with Klebsiella pneumoniae, the intramuscular injection of streptomycin alone sufficed to control the infection.

Other observers report serious injury to major peripheral nerves due to the toxic action of penicillin inadvertently injected too close to them.[17]

Prophylactic Use: Kuh and Collen [18] gave penicillin orally in doses of 100,000 to 400,000 units a day to a large group of persons and placebo tablets to an equal-sized group for a year to see whether the incidence of infections of the respiratory tract would be influenced. No significant difference was disclosed: Infections were just as prevalent in those treated with penicillin as in the controls. Reactions supposedly to penicillin occurred in about 10 per cent of the persons receiving the drug but, curiously, also in an only slightly smaller percentage of those receiving the placebo. The results of this study should go far in preventing the waste of penicillin in futile attempts to prevent colds and other infections.

Hirsch and his associates [19] gave penicillin in doses of 600,000 units to 65 patients before the extraction of teeth, whereas 65 controls were

14. Wilson, G.; Rupp, C., and Wilson, W. W.: The Dangers of Intrathecal Medication, J. A. M. A. **140**:1076-1079 (July 30) 1949.

15. Hoyne, A. L.: Intrathecal Therapy Contraindicated for Meningitis, Illinois M. J. **94**:295-298 (Nov.) 1948.

16. Zubrod, G.: Experimental Klebsiella Meningitis Treated with Intrathecal and Intramuscular Streptomycin, Bull. Johns Hopkins Hosp. **84**:461-469 (May) 1949.

17. Broadbent, T. R.; Odom, G. L., and Woodhall, B.: Peripheral Nerve Injuries from Administration of Penicillin, J. A. M. A. **140**:1008-1010 (July 23) 1949.

18. Kuh, C., and Collen, M. F.: Mass Penicillin Prophylaxis: An Experiment with Negative Results, J. A. M. A. **140**:1324-1328 (Aug. 27) 1949.

19. Hirsch, H. L.; Vivino, J. J.; Merril, A., and Dowling, H. F.: Effect of Prophylactically Administered Penicillin on the Incidence of Bacteremia Following Extraction of Teeth: Results in Patients with Healed Rheumatic and Bacterial Endocarditis, Arch. Int. Med. **81**:868-878 (June) 1948.

not treated. Bacteremia occurred in 37 per cent of those who received penicillin and in 46 per cent of the controls, a difference of only 9 per cent. However, alpha and gamma hemolytic streptococci were cultivated from 34 per cent of controls and from only 15 per cent of treated patients. Transient bacteremia occurred in 4 of 7 treated patients who had healed rheumatic valvular disease. Penicillin, therefore, cannot be relied on to prevent potentially serious bacteremia after dental or other operations.

Use for Gonorrhea: Eagle and his associates [20] prevented gonorrhea in men exposed to it by the oral administration of one tablet of 100,000 or 250,000 units of penicillin. Success can be obtained only when exposure to infection occurs within two to six hours after taking the tablet. Since the cocci multiply so rapidly, larger doses are needed when a longer interval occurs. No evidence of sensitization was found after giving penicillin once weekly for twenty-four weeks. Sensitization may occur when larger doses of 250,000 units are given daily. No penicillin-fast strains of gonococci were encountered during the study.

Aureomycin.—Although only a little over a year has elapsed at the time of this report since Duggan reported the isolation of aureomycin, it has received wide application and acclaim. It has certain advantages over other antibiotic drugs: It is effective when given orally, it is active against a wider range of bacteria and it is relatively nontoxic. Current knowledge of aureomycin is summarized in two papers.[21]

After oral administration, aureomycin appears in the blood and urine in effectively therapeutic amounts; it is present in the spinal fluid after parenteral or oral administration. In comparison with streptomycin, it is more efficient in an acid medium and it is less able to induce resistance of bacteria to itself. Although aureomycin is antibiotic for most gram-positive and gram-negative cocci, it is less active, weight for weight, than penicillin. In contrast, it is antibiotic for strains of Hemophilus and Rickettsia and for large particle "viruses" of the psittacosis-lymphogranuloma group. It has no effect on filtrable viruses except perhaps the supposed virus which causes viral pneumonia.

It is too soon to judge the relative therapeutic value of aureomycin and other antibiotics. It is effective in Rocky Mountain spotted fever, typhus and Q fever; venereal lymphogranuloma is well controlled with it. Most surprisingly, aureomycin is the first agent shown to be effective

20. Eagle, H., and others: Prevention of Gonorrhea with Penicillin Tablets, J. A. M. A. **140**:940-943 (July 16) 1949.

21. Finland, M.; Collins, H. S.; Gocke, T. M., and Wells, E. B.: Present Status of Aureomycin Therapy, Ann. Int. Med. **31**:39-52 (July) 1949. Spink, W. W., and Yow, E. M.: Aureomycin: Present Status in Treatment of Human Infections, J. A. M. A. **141**:964-966 (Dec. 3) 1949.

against viral pneumonia. Among patients with coccic diseases, those with pneumococcic pneumonia and meningococcemia responded well to therapy.[22] Because of its effectiveness in bacterial pneumonias and in some viral pneumonias, aureomycin may be the antibiotic of choice for pneumonia in general. It is also of value against staphylococcic infections, although Nichols and Needham [23] recommend its use routinely only if the cocci resist penicillin.

Among infections caused by gram-negative bacilli, aureomycin is said to be effective in brucellosis,[24] but, as discussed in the section on brucellosis, the results are not entirely satisfactory. Therapy in some cases of typhoid has been disappointing. Infections caused by Salmonella are not influenced.[21] Aureomycin is effective against most of the bacteria found in the urogenital tract except Proteus vulgaris (Bacillus proteus) and Pseudomonas aeruginosa (Bacillus pyocyaneus).[25] A combination of streptomycin and aureomycin is valuable at times. Aureomycin is perhaps as effective as streptomycin for the treatment of tularemia [26] and may be of value in pertussis,[27] in syphilis [28] and in amebiasis.[29]

In experimental animals aureomycin was more effective than penicillin in the treatment of relapsing fever and leptospirosis.[30]

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22. Collins, H. S.; Paine, T. F., and Finland, M.: Aureomycin in Treatment of Pneumococcal Pneumonia and Meningococcemia, Proc. Soc. Exper. Biol. & Med. **69**:263-265 (Nov.) 1948.

23. Nichols, D. R., and Needham, G. M.: Aureomycin in the Treatment of Penicillin-Resistant Staphylococcic Bacteremia, Proc. Staff. Meet., Mayo Clin. **24**: 309-315 (June 8) 1949.

24. Bryer, M. S., and others: The Treatment of Acute Brucellosis with Aureomycin, Bull. Johns Hopkins Hosp. **84**:444-460 (May) 1949. Knight, V., and others: Aureomycin in Typhus and Brucellosis, Am. J. Med. **6**:407-416 (April) 1949.

25. Rutenburg, A. M., and Schweinburg, F. B.: Aureomycin in Urinary Infections Due to Gram-Negative Organisms, Proc. Soc. Exper. Biol. & Med. **70**: 464-467 (March) 1949.

26. Woodward, T. E.; Roby, W. T.; Eppes, W.; Holbrook, W. A., and Hightower, J. A.: Aureomycin in Treatment of Experimental and Human Tularemia, J. A. M. A. **139**:831-832 (March 26) 1949.

27. Bell, J. A.; Pittman, M., and Olsen, B. J.: Pertussis and Aureomycin, Pub. Health Rep. **64**:589-598 (May 13) 1949.

28. O'Leary, P. A.; Kierland, R. R., and Herrell, W. E.: Oral Administration of Aureomycin and Its Effect on Treponema Pallidum in Man, Proc. Staff Meet., Mayo Clin. **23**::574-578 (Dec. 8) 1948.

29. McVay, L. V.; Laird, R. L., and Sprunt, D. H.: The Preliminary Report of the Successful Treatment of Amebiasis with Aureomycin, Science **109**:590-591 (June 10) 1949.

30. Heilman, F. R.: Aureomycin in the Treatment of Experimental Relapsing Fever and Leptospirosis Icterohaemorrhagica (Weil's Disease), Proc. Staff Meet., Mayo Clin. **23**:569-573 (Dec. 8) 1948.

Chloramphenicol (*Chloromycetin*®).—Since last year's review, mounting evidence has confirmed the value of chloramphenicol. It resembles aureomycin in the range of infectious agents it controls, its effectiveness when given orally and its relative lack of toxicity. Information concerning chloramphenicol is summarized by Woodward.[31] It is the first agent to give successful results in the treatment of typhoid, and it is as effective as aureomycin in the treatment of brucellosis. Typhus, scrub typhus, Rocky Mountain spotted fever and Q fever respond favorably to treatment with chloramphenicol. Trial in only a few patients suggests that chloramphenicol may be of value in treating viral pneumonia, relapsing fever, pertussis, some bacillary dysenteries and venereal lymphogranuloma. In experimentally infected animals chloramphenicol was effective against Vibrio comma[32] but not against Salmonella.[33] According to Smadel,[34] synthetic chloramphenicol, as prepared by Crooks and his associates, is as effective therapeutically as the substance derived from the mold.

New Antibiotics.—The search for new antibiotics continues apace. Waksman and others describe two: streptocin, which is active against trichomonas and gram-positive bacteria,[35] and neomycin, which is active against certain streptomycin-resistant bacteria, particularly Myobacterium tuberculosis.[36] Lupulon, an antibiotic derived from hops, is slightly bacteriostatic for Myco. tuberculosis in vitro, but when given to mice infected with tubercle bacilli it apparently controlled the infection in many.[37] Lupulon is fat soluble and probably is absorbed by the lipid fraction of the bacilli. It is even probable that antibiotics may be obtained from insects. Frings and his associates[38] report on the

31. Woodward, T. E.: Chloromycetin and Aureomycin: Therapeutic Results, Ann. Int. Med. **31**:53-82 (July) 1949.

32. Gauld, R. L., and others: Chloramphenicol (Chloromycetin) in Experimental Cholera Infection, J. Bact. **57**:349-352 (March) 1949.

33. Seligmann, E., and Wassermann, M.: Action of Chloromycetin on Salmonella, Proc. Soc. Exper. Biol. & Med. **71**:253-255 (June) 1949.

34. Smadel, J., and others: Comparison of Synthetic and Fermentation Chloramphenicol (Chloromycetin) in Rickettsial and Viral Infections, Proc. Soc. Exper. Biol. & Med. **70**:191-194 (Feb.) 1949.

35. Waksman, S. A., and others: Streptocin, Antibiotic Isolated from Mycelium of Streptomyces Griseus, Active Against Trichomonas Vaginalis, and Certain Bacteria, Proc. Soc. Exper. Biol. & Med. **70**:308-312 (Feb.) 1949.

36. Waksman, S. A., and Lechevalier, H. A.: Neomycin: A New Antibiotic Active Against Streptomycin Resistant Bacteria, Including Tuberculosis Organisms, Science **109**:305-307 (March 25) 1949.

37. Chin, Y. C.; Anderson, H. H.; Alderton, G., and Lewis, J. C.: Antituberculous Activity and Toxicity of Lupulon for the Mouse, Proc. Soc. Exper. Biol. & Med. **70**:158-162 (Jan.) 1949.

38. Frings, H.; Goldberg, E., and Arentzen, J. C.: Antibacterial Action of the Blood of the Large Milkweed Bug, Science **108**:689-690. (Dec. 17) 1948.

antibacterial effect of the blood of the milkweed bug and cite other studies concerning antibiotics in grasshoppers and in the feces of blowfly maggots.

VIRAL DISEASES

Horsfall [39] discusses the mechanism by which viruses enter cells and cause disease. The process theoretically occurs in five steps: (1) contact of the virus and the susceptible cells (apparently a newly discovered co-factor is required before union is possible) and (2) alteration of the surface of the cell; these permit (3) penetration of the cell, (4) multiplication of the virus and (5) the release of newly formed particles of virus. On these factors must be based measures to control viral diseases. Disinfectants are unlikely to be of value. Viruses of medium and small size are unaffected by sulfonamide drugs, penicillin, streptomycin or chloramphenicol. For the prevention or therapy of a viral infection there are several possible modes of attack: specific vaccination, the blockage of some metabolic system of the host cell essential for the multiplication of the virus, the interference phenomenon and the induction of nutritional deficiency. A degree of nutritional deficiency results in greater resistance to viral infections presumably owing to a subnormal metabolic state in the cells which is not conducive to growth of a virus. Horsfall's experiments indicate that certain complex carbohydrates or polysaccharides of bacterial or other origin inhibit the growth of a few viruses, probably by inducing changes in the metabolism of the host cell and competing with the virus. This behavior may provide a new line of therapeutic attack.

By using infectious ectromelia of mice, a virus disease closely related to vaccinia and smallpox, Fenner [40] critically reinterprets the pathogenesis of the acute exanthematous diseases of man. In the usual textbook description, the symptoms of smallpox and measles, for example, are usually divided into the period of incubation, the period of invasion and the stage of eruption. The period of onset of symptoms, however, does not represent the stage of invasion, and there is no evidence of any role played by allergy in the development of the rash. According to the author's observations a complicated series of events occurs between the entry of the virus and the end of the incubation period: The virus reaches the regional lymph nodes and multiplies there; virus then escapes into the blood stream, undergoes phagocytosis and multiplies in the endothelium-rich organs, where necrosis of the invaded cells and liberation of more virus causes secondary viremia; the virus thus distributed reaches the cells of the epidermis. Invasion, growth

39. Horsfall, F. L.: Prospects for the Control of Viral Diseases by Chemical Agents, Canad. M. A. J. **66**:439-447 (May) 1949.

40. Fenner, F.: The Pathogenesis of the Acute Exanthem, Lancet **2**:915-920 (Dec. 11) 1948.

and dispersion therefore take place during the so-called incubation period, and symptoms begin when virus multiplies to its maximum level and causes necrosis of cells; the secondary viremia resulting from the necrosis of cells then carries the virus to the skin, where multiplication again requires a few days before the eruption appears.

These conclusions have a direct bearing on Horsfall's views just discussed, namely, that successful therapy must attack the infection in the early period before necrosis of cells, secondary viremia and symptoms take place. How to diagnose viral diseases in the early period before their clinical characteristics develop is a challenge to be met.

Andrewes [41] succeeded in preventing infection with influenza A virus in ferrets by inoculating them first with influenza B virus, thus involving the interference phenomenon. Protection is effective only so long as apparent or inapparent infection with the first-introduced virus is active.

Studies with the electron microscope revealed elementary bodies in the vesicular and spinal fluid from patients with herpes zoster.[42] The size of the bodies was smaller than that of chickenpox virus and larger than that of herpes simplex virus. Bang and Gey [43] had success in revealing particles of equine encephalomyelitis virus in chains and clumps which strongly resembled minute diplococci. Multiplication appeared to take place by fission. Preparations of tissue culture were satisfactorily studied with the electron microscope. Angulo and others [44] demonstrated the viruses of yellow fever, herpes simplex, fowlpox and distemper in unstained tissue with special high contrast phase photomicrographs. That they are distinguishable by this method may be of diagnostic value.

Influenza.—There is international cooperation for the study of influenza among the World Influenza Center in London, under the direction of Dr. C. H. Andrewes, the United States Public Health Service and various foreign centers.[45] In the United States the Strain

41. Andrewes, C. H.: Prophylaxis of Virus Infections, with Special Reference to the Use of Vaccines, Brit. M. J. **2**:1007-1009 (Dec. 11) 1948.

42. Evans, A. S., and Melnick, J. L.: Electron Microscope Studies of the Vesicle and Spinal Fluids from a Case of Herpes Zoster, Proc. Soc. Exper. Biol. & Med. **71**:283-286 (June) 1949.

43. Bang, F. G., and Gey, G. O.: Electron Microscopy of Tissue Cultures Infected with the Virus of Eastern Equine Encephalitis, Proc. Soc. Exper. Biol. & Med. **71**:78-80 (May) 1949.

44. Angulo, J. J.; Richards, O. W., and Roque, A. L.: Demonstration of Viral Inclusion Bodies in Unstained Tissue Sections with the Aid of the Phase Microscope, J. Bact. **57**:297-303 (March) 1949.

45. Culbertson, J. T.: Plans for United States Cooperation with the World Health Organization in the International Influenza Study Program, Am. J. Pub. Health **39**:37-43 (Jan.) 1949.

Study Center at Cornell University Medical College in New York, under the direction of Dr. T. P. Magill, has been designated as the National Center for the United States, and an Influenza Information Center has been established at the National Institute of Health, Bethesda, Md., to cooperate with the World Health Organization and with the World Influenza Center in London.[46] The function of the organization is to to serve as a clearing house for information on influenza, to identify and study new strains of virus and to aid in the improvement of influenza vaccine. All epidemics of influenza or influenza-like disease should be reported to the Influenza Information Center, and specimens of virus and/or blood from patients should be sent to it or to a conveniently located laboratory for identification. A list of cooperating laboratories is published in Culbertson's paper [45] and in a special report.[46]

A widespread epidemic of influenza in Europe was first detected in December 1948 in Italy. In January it appeared to spread northward to Austria, France and the Low Countries.[47] England escaped. Clinically the disease was mild. A few complications occurred; these were chiefly caused by staphylococci. In Holland the attack rate was 7 per cent, and the mortality rate, 0.3 per cent.[48] The causative virus, according to Andrewes and others, was of the A group, closely related to the FM 1 virus isolated in England and in the United States in 1947 but different from the PR 8 strain. B virus was also encountered.

The experience of Meiklejohn and Bruyn [49] with two epidemics of influenza in California reemphasizes the instability of the causative viruses. Although the serum of relatively few persons tested contained antibody, the epidemic was mild. The virus strains isolated during the epidemics were similar and of the A group but differed greatly from the previously isolated A strains. Poor antibody responses were obtained by vaccination with viruses of the new types. These results and the unpredictability of appearance of still more new types greatly complicate any specific measures for prophylaxis.

Variations apparently also occur, as might be expected, among B strains of virus. Lazarus [50] isolated three strains of B virus during an

46. Influenza Information Center Established, Government Services, J. A. M. A. **139**:107 (Jan. 8) 1949.

47. Influenza Epidemic in Europe, Government Services, J. A. M. A. **139**: 316 (Jan. 29) 1949.

48. Influenza Research, Foreign Letters, Netherlands, J. A. M. A. **140**:642-643 (June 18) 1949.

49. Meiklejohn, G., and Bruyn, H. B.: Influenza in California During 1947 and 1948, Am. J. Pub. Health **39**:44-49 (Jan.) 1949.

50. Lazarus, A. S.: Isolation of Three Strains of Type B Influenza Virus Incompletely Related to Lee, Proc. Soc. Exper. Biol. & Med. **71**:317-319 (June) 1949.

epidemic of influenza in Seattle which were not identical with the standard B virus.

Francis and his associates [51] found a strain of swine influenza virus isolated in 1939 to resemble antigenically some strains of "A-prime" virus of human origin; serum from patients during an epidemic in 1947 contained antibody for the swine influenza virus as well. The question is unsettled whether the swine or man serves as the original source of infection, renewing interest in the speculations of Koen and Shope as regards the origin of the 1918-1919 pandemic. The designation of the newly isolated strain as "A-prime" has given rise to controversy over nomenclature.

The enigma of where influenza virus resides in interepidemic periods is unsolved. Taylor,[52] in a study of an institutional population, found virus in the throat of symptomless persons thirty-two days before, and of course during, an epidemic but not at other times. Commercial influenza A and B vaccine had no effect in preventing the disease.

Maxwell and his associates [53] found influenza virus or serologic evidence of its activity in 17 of 36 patients with pneumococcic pneumonia during an epidemic of influenza. The virus was of the kind which caused other nonpneumonic instances of influenza. Influenza virus was isolated from only 1 of 33 patients with bacterial pneumonia in an interepidemic period, and the pneumonic lungs of 4 patients in which no bacteria at all were found yielded influenza virus. It appears therefore that, as long believed, the virus may predispose affected tissue to invasion by pathogenic bacteria or may in rare cases itself cause severe pneumonia.

A study of freshly isolated strains of virus with the electron microscope [54] confirmed Wykoff's description of filamentous forms which at first were regarded by many as artefacts. On passage in eggs or mice the long filamentous forms became less numerous and were replaced by the better known round or intermediate forms. Without much doubt they represent the virus itself.

The Common Cold.—Knowledge regarding colds is static. Andrewes [55] summarizes the results of studies at the Common Cold

51. Francis, T.; Quilligan, J. J., and Minuse, E.: Resemblance of a Strain of Swine Influenza Virus to Human A-prime Strains, Proc. Soc. Exper. Biol. & Med. **71**:216-220 (June) 1949.

52. Taylor, R. M.: Studies on the Survival of Influenza Virus Between Epidemics and Antigenic Variants of Virus, Am. J. Pub. Health **39**:171-178 (Feb.) 1949.

53. Maxwell, E. S.; Ward, T. G., and Van Metre, T. E., Jr.: The Relation of Influenza Virus and Bacteria in the Etiology of Pneumonia, J. Clin. Investigation **28**:307-318 (March) 1949.

54. Morphology of 1949 Influenza, Government Services, J. A. M. A. **139**: 1090 (April 16) 1949.

55. Andrewes, C. H.: The Natural History of the Common Cold, Lancet **1**:71-73 (Jan. 8) 1949.

Research Unit at Harvard Hospital, Salisbury, England, and restates the perennial problems in a series of questions: (1) Is the common cold an entity or a group of diseases? (2) Is it caused by viruses or bacteria or neither? (3) How long does the causative agent persist in the host or elsewhere? (4) Can infection be caught from a victim, or is it activated in a person who harbors the agent? (5) If the agent is contagious, how is it spread? (6) If it can be activated, what activates it? 7. What accounts for seasonal incidence? (8) Why does resistance vary from person to person and in one person at different times? These unanswered questions indicate our dearth of knowledge.

In the Salisbury studies on colds, elaborately planned to avoid as much error as possible involving cross infections and other difficulties, the syndrome of the common cold was induced in 60 per cent of volunteer subjects. Filtered and unfiltered nasal washings from persons with colds were used. Colds were found to be transmissible when washings were taken even before symptoms developed. The size of the virus particle was estimated as between 20 to 50 millimicrons in diameter. None of a large variety of animals could be infected. Even the volunteer human subjects, the only test "animals" susceptible to colds besides chimpanzees, were too resistant and too variable for satisfactory experiments. No evidence of the cultivation or survival of the virus on culture tests was obtained, in contrast to reports of such success by three American groups. It is possible that a different virus was dealt with.

It is concluded that colds are probably caused by viruses which constantly pass from one person to another, usually causing no symptoms or only mild ones. A real cold develops only in a person whose local "resistance" is temporarily low. From such a person the virus is disseminated in large amounts, but few persons harbor it long and it probably dies out soon.

Atlas and Hottle [56] have tested a new method to detect the presence of the supposed virus which causes the common cold. Heretofore the only evidence of its presence came by transmission of the infection to volunteers. The authors describe a procedure with tryptophane and perchloric acid which gives a color reaction only in the fluids which caused colds in volunteers, indicating the presence of virus. By titration, a quantitative estimate of the amount of virus in cultures in embryonated eggs can be made. The observations have not been confirmed by others. Extensive studies on the common cold are under way at present under the direction of Dr. Topping at the National Institute of Health.[57]

56. Atlas, L. T., and Hottle, G. A.: The Common Cold: Titration of MR-1 Virus in Embryonated Eggs, Science **108**:743-745 (Dec. 31) 1948.

57. Topping, N. H.: Research on the Common Cold, Bull. New York Acad. Med. **25**:530-533 (Aug.) 1949.

A group of workers [58] still expresses interest in the illogical idea of treating a variety of chronic infections of the respiratory tract with autogenous vaccine or bacterial filtrates. The agents are injected intracutaneously or, worse still, directly into the nasal sinuses. Influenza vaccine had no influence in preventing attacks of the common cold.[59]

Viral Pneumonia.—Evidence has been published of the value of aureomycin and chloramphenicol in viral pneumonia.[60] In a controlled study by Meiklejohn and Shragg [61] there seemed to be no question that aureomycin shortened the severe form of the disease in 22 patients as compared with 20 treated with penicillin. The cold agglutination test gave positive results in most patients. The average dosage of aureomycin was 1 Gm. orally every six hours. Nausea and vomiting accompanied therapy in half the patients. Much more study is necessary before final appraisal of the value of these antibiotics for viral pneumonia is possible. If they prove to be of value, it will show one of two things: They are the first ones available to attack viruses, or "viral" pneumonia is not caused by a virus. In unpublished studies by others, aureomycin had no effect in some viral pneumonias even when cold agglutination was demonstrated. Some cases in which benefit was obtained proved later to have been instances of fever or psittacosis.

Adams [62] describes sporadic cases of viral pneumonitis in infancy in addition to the epidemics he observed previously. In retrospect he maintains that during the epidemics all stages of severity were noted, but that the minor ones with cough and sneezing but without pneumonia were disregarded; many other observers still choose to do this. The disease in infants seemed in some instances to have been contracted from adults with mild infection of the upper respiratory tract. These observations match exactly the clinical, pathologic and epidemiologic observations I made in 1938 in first describing viral pneumonia as such in adults. An important difference in Adams' patients was the presence of cytoplasmic inclusion bodies in the epithelial cells of the entire pulmonary tree. The significance of the inclusion bodies is not yet clear.

58 Kinghorn, H. M.; Wilson, G. E., and Dworski, M.: Bacterial Filtrates and Autogenous Vaccines in the Treatment of Chronic Sinus Disease and Other Chronic Respiratory Affections: Preliminary Report, New York State J. Med. **49**:41-45 (Jan. 1) 1949.

59. Blanton, W. B., and Sutphin, A. K.: Influenza Virus Vaccine, Types A and B: Experience with It in Cold Prevention, Virginia M. Monthly **75**:607-609 (Dec.) 1948.

60. Schoenbach, E. B., and Bryer, M. S.: Treatment of Primary Atypical Nonbacterial Pneumonia with Aureomycin, J. A. M. A. **139**:275-280 (Jan. 29) 1949. Kneeland, Y.; Rose, H. M., and Dillon, C. D.: Aureomycin in the Treatment of Primary Atypical Pneumonia, Am. J. Med. **6**:41-50 (Jan.) 1949.

61. Meiklejohn, G., and Shragg, R. I.: Aureomycin in Primary Atypical Pneumonia: A Controlled Evaluation, J. A. M. A. **140**:390-396 (May 28) 1949.

62. Adams, J. M.: Primary Pneumonitis in Infancy, J. A. M. A. **138**:1142-1144 (Dec. 18) 1948.

Inclusion bodies were also found by DeBerardinis [63] in adults with minor infections of the respiratory tract.

The cold agglutinin test and the test for Streptococcus MG agglutinins gave positive results in about 80 per cent of 89 patients with viral pneumonia; the serologic test for the psittacosis group of viruses was positive in 5 per cent, but in none was evidence of Q fever encountered.[64] A review of the etiology of the viral pneumonias with special reference to European contributions has been published.[65]

Other Pneumonias.—A psittacosis-like virus apparently identical with the meningopneumonitis virus described by Francis and Magill in 1938 was isolated from the lung of a patient who died of pneumonia.[66] Because of the close relationship of this group of agents, the authors believe it best to name them all psittacosis-like viruses. Since the agents require living cells for multiplication, the authors suggest the term "cytomicrobes" to distinguish them from viruses and bacteria. To find whether or not psittacosis is transmitted congenitally from bird to bird, Davis and Vogel [67] infected hen's eggs; the hatched chickens harbored the agent for three weeks. In this paper is used the new name for the causative agent which probably will mildly shock nomenclators or philologists, namely Myagawanella psittaci. The reader also may be amused by a Japanese-German-Latin hybrid term, Shigella schmitzii (*Lancet* **1:** 220, 1949). Incidentally, here are a few more new and romantic terms which are introduced in the 1947 edition of Bergey's "Manual of Determinative Bacteriology": The virus of poliomyelitis is called Legio debilitans; the virus of yellow fever is Charon evagatus (after Charon, ferryman of the Lower World), and influenza viruses A and B are Tarpeia alpha and beta respectively (Tarpeia after the Roman maiden who opened the citadel to the enemy).

Ornithosis.—As may have been predicted from the studies of Meyer and Eddie, ornithosis was recognized in 8 patients who had been in contact with ducks in the large commercial duck farms on Long Island.[68] The disease was mild to moderately severe; all patients recovered.

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63. DeBerardinis, C.: Intracellular Inclusion Bodies in Mild Disease of the Respiratory Tract, Arch. Path. **45**:360-365 (March) 1948.

64. Morgan, H. R., and Finland, M.: Serologic Findings in Patients with Primary Atypical Pneumonia, Am. J. Clin. Path. **18**:593-597 (Aug.) 1948.

65. Kikuth, W., and Gönnert, R.: Zur Aetiologie der primären atypischen Pneumonie oder Viruspneumonie, Klin. Wchnschr. **27**:185-188 (March 15) 1949.

66. deGara, P. F., and Furth, J.: Pneumonia Produced by a Meningopneumotropic Virus, Arch. Path. **45**:474-493 (April) 1948.

67. Davis, D. J., and Vogel, J. E.: Recovery of Psittacosis Virus from Chickens Hatched from Inoculated Eggs, Proc. Soc. Exper. Biol. & Med. **70**:585-586 (April) 1949.

68. Wolins, W.: Ornithosis (Psittacosis): Review with Report of Eight Cases Resulting from Contact with Domestic Pekin Duck, Am. J. M. Sc. **216**: 551-564 (Nov.) 1948.

Morgan and Finland [69] isolated herpes virus from the lung of a patient who had erythema multiforme with pneumonia. Its presence in large amount suggested a causal relationship. However, there were no inclusion bodies present, and no virus was isolated from the lung in another similar case. The virus may have been a commensal, as it often is.

Measles Pneumonia.—Pneumonia occurred in 25 per cent of 163 patients with measles, most commonly under the age of 5 years.[70] About half showed evidence of pneumonia, probably caused by the virus itself, in the early eruptive stage. Gram-positive cocci were frequent secondary invaders and caused serious disease, but they were controlled with penicillin.

Cave Sickness.—In 1947, Cain and his associates described a peculiar viral pneumonia-like disease in soldiers who had briefly occupied a cellar in Oklahoma. More recently Washburn's group [71] recorded a similar outbreak among persons who explored a cave in Arkansas. The cause is unknown.

Poliomyelitis.—According to Bodian's review [72] of older work and his recent tests, reinfection with poliomyelitis cannot be caused by the same virus which caused the first attack. Reinfection can easily be caused experimentally by injection of poliomyelitis virus of a different immunologic type, but it is usually less severe, indicating that low grade overlapping immunity persisted after the first infection. It is obvious, then, that second attacks of poliomyelitis may occur in man but that they are caused by virus different from that of the first infection.

Bodian, Morgan and Howe [73] report the classification of fourteen slightly different strains of poliomyelitis virus into three basic immunologic types.

Summer Epidemic Diseases.—Little progress has been made in knowledge of the epidemics of mild diseases which occur in the summer months. They have been called summer flu, summer grip, summer diarrhea and other terms. Several have, of course, been recognized as

69. Morgan, H. R., and Finland, M.: Isolation of Herpes Virus from a Case of Atypical Pneumonia and Erythema Multiforme Exudativum, Am. J. M. Sc. **217**:92-95 (Jan.) 1949.

70. Weinstein, L., and Franklin, W.: The Pneumonia of Measles, Am. J. M. Sc. **217**:314-324 (March) 1949.

71. Washburn, A. M.; Tuohy, J. H., and Davis, E. L.: Cave Sickness: A New Disease Entity? Am. J. Pub. Health **38**:1521-1526 (Nov.) 1948. A New Pulmonary Disease Entity? Current Comment, J. A. M. A. **139**:232 (Jan. 22) 1949.

72. Bodian, D.: Differentiation of Types of Poliomyelitis Virus: I. Reinfection Experiments in Monkeys (Second Attacks), Am. J. Hyg. **49**:200-218 (March) 1949.

73. Bodian, D.; Morgan, I. M., and Howe, H. A.: Differentiation of Types of Poliomyelitis Virus: III. The Grouping of Fourteen Strains into Three Basic Immunological Types, Am. J. Hyg. **49**:234-245 (March) 1949.

poliomyelitis, viral dysentery and influenza, but others are still obscure. Recently several groups of observers have thrown more light on the problem. A large epidemic in Cincinnati in 1947, at first called summer grip or summer sore throat, is shown by Sabin and Steigman [74] to have been caused by a poliomyelitis virus of low virulence. About 10,000 persons, chiefly at ages of 1 to 10 years, presumably had the disease. There were no symptoms of involvement of the respiratory tract. Not more than 40 cases of poliomyelitis were recorded at the time, but the number increased to 170, 55 of which were paralytic, after the mild epidemic disease declined. From the patients, poliomyelitis virus of high virulence was obtained. Apparently there were two strains of virus rampant, one of low virulence and the other of high virulence.

In studies by Curnen's group,[75] an agent similar to the one reported by Dalldorf and Sickles in 1948 was isolated from the feces of patients thought to have had nonparalytic poliomyelitis, aseptic meningitis or fever of unknown origin. At least two immunologic types of the virus were found, and specific neutralizing antibodies were developed in the patients' serum. The virus was widespread in this country, being present in Ohio, North Carolina and New England. It was present in samples of sewage and in flies.

What may be a similar type of disease was described to me by Prof. Anton Hittmair. An explosive epidemic of mild disease occurred in the course of two or three weeks, affecting about 300 persons in the small city of Hall near Innsbruck, Austria. The symptoms were a sudden onset of headache, fever, malaise, nausea, vomiting, diarrhea and stiffness of the neck. Pleocytosis—as many as 1,000 cells per cubic millimeter were noted—occurred in the spinal fluid. The disease lasted two or three days, and all victims recovered without paralysis or other sequelae. The cause was not discovered.

Webb and his associates [76] studied an outbreak of a mild epidemic disease in Louisiana, particularly among children, called a summer disease, or three day fever.[76] They point out the probability of the existence of a number of hitherto unrecognized mild diseases, probably viral in origin, and state that viruses which cause mild disease in adults may cause severer reactions in children. The source of the epidemic in question could not be traced; it was probably air borne. Clinically there were a sudden onset of moderate to high fever, severe headache, myalgia

74. Sabin, A. B., and Steigman, A. J.: Poliomyelitis Virus of Low Virulence in Patients with Epidemic "Summer Grip or Sore Throat," Am. J. Hyg. **49**:176-193 (March) 1949.

75. Curnen, E. C.; Shaw, E. W., and Melnick, J. L.: Disease Resembling Nonparalytic Poliomyelitis Associated with a Virus Pathogenic for Infant Mice, J. A. M. A. **141**:894-901 (Nov. 26) 1949.

76. Webb, C. H., Wolfe, S. G., and Simpson, V.: Clinical Features of a Summer Disease (Three-Day Fever) Apparently of Virus Etiology, New Orleans M. & S. J. **101**:249-256 (Dec.) 1948.

and notable absence of any disturbance of the respiratory or gastrointestinal tract. Several cases of poliomyelitis were discovered in the community during the epidemic, but the epidemic disease almost certainly was not poliomyelitis. Serum from several children was shown to contain neutralizing antibodies against the virus of Newcastle disease.

It is clear that a number of mild epidemic diseases remain to be delineated. Confusion of nonparalytic poliomyelitis with mumps is discussed in the section on Mumps and Poliomyelitis.

Encephalitis.—Since the injection of brain tissue into animals causes disseminated encephalomyelitis resembling the demyelinating lesions in human encephalomyelitis and that which occasionally occurs after antirabies vaccination, Kirk and Ecker [77] suggest that antibodies to human brain develop in persons who receive Semple antirabies vaccine. Postvaccinal encephalitis therefore may be noninfectious in origin. According to VanBogaert,[78] the postvaccinal encephalitis occurring after smallpox vaccination and that following chickenpox, measles and scarlet fever are also the result of an anaphylactic phenomenon or a hyperallergic reaction of cerebral tissue. An observation supporting these views was made by Pickar and Kramer [79] on a patient in whom encephalomyelitis developed after vaccination. They demonstrated a strong reaction of the skin to the intradermal injection of vaccine in a high dilution. Prompt improvement occurred after the administration of diphenhydramine hydrochloride (benadryl hydrochloride®). The reaction of the skin was suppressed with tripelennamine hydrochloride.

Rabies vaccine free from allergen has been prepared.[79a]

The first 3 cases of natural infection with the virus of louping ill, a disease of sheep in Scotland, are reported.[80] The disease gives a clinical picture of meningoencephalitis preceded by an influenza-like infection. It may be the same as, or similar to, Russian spring and summer encephalitis and probably occurs oftener than was believed among persons in contact with sheep and sheep ticks.

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77. Kirk, R. C., and Ecker, E. E.: Time of Appearance of Antibodies to Brain in the Human Receiving Anti-Rabies Vaccine, Proc. Soc. Exper. Biol. & Med. **70**:734-737 (April) 1949.

78. VanBogaert, L.: Encephalitis Following Jennerian Vaccination Compared to That Following Exanthems, Act. clin. belg. **3**:461-493 (Nov.-Dec.) 1948.

79. Pickar, D. N., and Kramer, H. M.: Encephalitis Complicating Vaccination for Rabies: A Case Treated with Antihistaminic Agents, South. M. J. **42**:127-129 (Feb.) 1949.

79a. Bell, J. F., Wright, J. T., and Habel, K.: Rabies Vaccine Freed of Factor Causing Allergic Encephalitis, Proc. Soc. Exper. Biol. & Med. **70**:457-463 (March) 1949.

80. Davison, G.; Neubauer, C., and Hurst, E. W.: Meningo Encephalitis in Man Due to the Louping-Ill Virus, Lancet **2**:453-456 (Sept. 18) 1948. Brewis, E. G.; Neubauer, C. A., and Hurst, E. W.: Another Case of Louping-Ill in Man: Isolation of the Virus, ibid. **1**:689-691 (April 23) 1949.

The virus of eastern equine encephalomyelitis was isolated in Tennessee for the first time from chicken mites and chicken lice,[81] and in Georgia from naturally infected mosquitoes (Mansonia perturbans).[82] Neutralizing antibodies were present in the serum of several chickens and a cow.

Zichis and Piszczek investigated the possibility of the transmission of neurotropic virus in drinking water contaminated by back siphonage.[83] The viruses of lymphocytic choriomeningitis, poliomyelitis, equine encephalomyelitis and St. Louis encephalitis survived for several days after exposure to chlorinated water in a plumbing system. Faulty plumbing and back siphonage, therefore, may provide means for transmission of these agents.

Rabies.—At a recent conference on rabies, the control of the disease in New York state was said to be directed chiefly toward mass vaccination of dogs.[84] In that state the chief source of rabies seems to be in foxes, which should be reduced in number by professional trappers. Rabid cattle are not important as transmitters of infection. A unified, nationwide program is necessary for the control of rabies, since it appears to be increasing in incidence.[85] Each year as a result of exposure to the disease about 30,000 persons are subjected to the painful, hazardous and often unnecessary series of inoculations with vaccine.

Mumps.—With the development of serologic and other tests and by studies of experimentally infected children, many of the previous views and conclusions in regard to the spread of mumps virus have been confirmed: Inapparent infections occur; diagnosis of mumps without parotitis can be made; virus is present in the saliva several days before clinical evidence of disease appears and persists as long as six days after the onset of disease, and virus is present in the spinal fluid during mumps meningoencephalitis.[86] Persons with inapparent infections may shed virus in their saliva and be responsible for spreading the disease.

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81. Howitt, B. F.; Dodge, H. R.; Bishop, L. K., and Gorrie, R. H.: Virus of Eastern Equine Encephalomyelitis Isolated from Chicken Mites (Demanyssus Gallinae) and Chicken Lice (Eomenacanthus Stramineus), Proc. Soc. Exper. Biol. & Med. **68**:622-625 (July-Aug.) 1948.

82. Howitt, B. F.; Dodge, H. R.; Bishop, L. K., and Gorrie, R. H.: Recovery of the Virus of Eastern Equine Encephalomyelitis from Mosquitoes (Mansonia Perturbans) Collected in Georgia, Science **110**:141-142 (Aug. 5) 1949.

83. Zichis, J., and Piszczek, E. A.: Duration and Viability of Neurotropic Viruses in an Experimental Plumbing System Contaminated by Back-Siphonage, Science **108**:503-505 (Nov. 5) 1948.

84. Control of Rabies, Current Comment, J. A. M. A. **139**:1083 (April 16) 1949.

85. Steele, J. H., and Tierkel, E. S.: Rabies Problems and Control: A Nation-Wide Program, Pub. Health Rep. **64**:785-796 (June 24) 1949.

86. Henle, G.; Henle, W.; Wendell, K. K., and Rosenberg, P.: Isolation of Mumps Virus from Human Beings with Induced Apparent and Inapparent Infections, J. Exper. Med. **88**:223-232 (Aug.) 1948.

Mumps virus was isolated for the first time from the blood of a patient in a study of experimentally infected children.[87] The virus was excreted in the saliva from the eleventh to the fifteenth day after exposure, that is, two to six days before symptoms or signs appeared and for four days afterward. Patients with orchitis alone and 6 of 8 children with inapparent disease had virus in the saliva fifteen days after infection; it was then demonstrable for one to nine additional days.

Henle and her co-workers [88] demonstrated that chick embryo antigen consists of two separate antigens, V and S. Both can be demonstrated in the serum of patients with clinical and subclinical mumps and may prove to be helpful diagnostic aids, especially in unusual cases with encephalitis and in those without parotitis.

Diethylstilbestrol U. S. P. given orally in doses of 2 mg. daily prevented the development of orchitis in adult patients with mumps.[89] Doses of 5 mg. during orchitis caused decided improvement with lessening of pain and recovery in an average of 4.7 days.

Mumps and Poliomyelitis.—Kilham and his associates [90] point out the impossibility of differentiating mumps encephalitis and nonparalytic poliomyelitis on clinical or epidemiologic grounds. No laboratory aid is available for routine diagnosis of nonparalytic poliomyelitis. Of 17 patients suspected of having poliomyelitis, 6 actually had mumps meningoencephalitis without parotitis or orchitis. Mumps virus was recovered from the spinal fluid of 3 of these patients.

Rubella.—The menace of rubella in early pregnancy prompted Anderson [91] and Burnet [91a] to study the infection. No success in cultivating the agent was attained, but the disease was transmitted to 11 of 25 volunteers who inhaled nebulized throat washings from patients. The incubation period averaged sixteen days. The virus is evidently present in the throat during the eruptive stage. It can be preserved at —70 C., passes through an 800 millimicron membrane and is unaffected by penicillin. It is possible, therefore, to induce the infection at will in most susceptible

87. Kilham, L.: Isolation of Mump Virus from the Blood of Six Patients, Proc. Soc. Exper. Biol. & Med. **69**:99-100 (Oct.) 1948.

88. Henle, G.; Harris, S., and Henle, W.: The Reactivity of Various Human Sera with Mumps Complement-Fixation Antigens, J. Exper. Med. **88**:133-147 (July) 1948.

89. Hoyne, A. L.; Diamond, J. H., and Christian, J. R.: Diethylstilbestrol in Mumps Orchitis: Prophylactic and Therapeutic Use, J. A. M. A. **140**:662-665 (June 25) 1949.

90. Kilham, L.; Levens, J., and Enders, J. F.: Nonparalytic Poliomyelitis and Mumps Meningoencephalitis: Differential Diagnosis, J. A. M. A. **140**:934-936 (July 16) 1949.

91. Anderson, S. G.: Experimental Rubella in Human Volunteers, J. Immunol. **62**:29-40 (May) 1949.

91a. Studies in the Transmission of Rubella, Foreign Letters, J. A. M. A. **139**:731 (March 12) 1949.

young women to avert an attack later during pregnancy. Preliminary studies indicate the possible value of "convalescent" concentrated gamma globulin as a prophylactic agent.

Yellow Fever.—Immunity to yellow fever endures for at least six years after vaccination with the 17 D strain of virus.[92] For the first time since 1905, yellow fever was recognized in Panama. Eight cases and 6 deaths were recorded. Large amounts of vaccine were promptly sent to the area.

Smallpox.—As a result of the alarm caused by a few cases of smallpox in New York city in 1947, about 5,000,000 persons were vaccinated.[93] A random sampling of the reaction which followed indicated 74 per cent of the persons to be susceptible. Forty-five instances of postvaccinal encephalitis and 4 deaths were recorded. Forty-five other patients, 28 of whom had had a dermatosis, had generalized vaccinia. Of these 45, 28 had not been vaccinated but had had intimate contact with some one recently vaccinated. No increase in congenital defects was noted in infants born to women vaccinated in the first four months of pregnancy; results of other studies bear out this observation.[94]

Newcastle Disease.—Although Newcastle disease of fowl is worldwide in distribution, few authentic cases have been reported in man. The studies of Howitt and others,[95] in which antibodies against Newcastle virus were found in children after unexplained febrile disease, are suggestive but the virus was not isolated. Freymann and Bang [96] report 3 cases of conjunctivitis and preauricular lymphadenitis presumably caused by Newcastle virus accidentally acquired in a laboratory. McGough [97] studied 10 patients who ate chicken and had nausea, vomiting, fever, malaise, abdominal pain and headache two and a half to five days later, caused, the author believes, by Newcastle virus. Neutralization tests were said to give positive results. The clinical picture in all 3 reports discussed was different: Howitt's patients showed evidence of involvement of the central nervous system and McGough's had gastrointestinal disturbances. One wonders whether the patients did not have

92. Dick, G. W. A., and Smithburn, K. C.: Immunity to Yellow Fever Six Years After Vaccination, Am. J. Trop. Med. **29**:57-62 (Jan.) 1949.

93 Greenberg, M.: Complications of Vaccination Against Smallpox, Am. J. Dis. Child. **76**:492-502 (Nov.)1948.

94. Bellows, M. T.; Hyman, M. E., and Merritt, K. K.: Effect of Smallpox Vaccination on the Outcome of Pregnancy, Pub. Health Rep. **64**:319-323 (March 11) 1949.

95. Howitt, B. F.; Bishop, L. K., and Kessling, R. E.: Presence of Neutralizing Antibodies of Newcastle Disease Virus in Human Sera, Am. J. Pub. Health **38**:1263-1272 (Sept.) 1948.

96. Freymann, M. W., and Bang, F. G.: Human Conjunctivitis Due to Newcastle Virus in the U. S. A., Bull. Johns Hopkins Hosp. **84**:409-413 (May) 1949.

97. McGough, T. F.: Outbreak of Newcastle Virus Disease in Tuscarawas County, Ohio, Ohio State M. J. **45**:25-26 (Jan.) 1949.

some other diseases instead. Conjunctivitis apparently is characteristic of the disease in man, since Ingalls and Mahoney [97a] describe 2 other patients from whom the virus was isolated.

A hemolysin similar to that of mumps virus was associated with Newcastle disease virus.[98] This factor and the ability to agglutinate erythrocytes of certain animals or birds suggest a relationship between the two viruses and also with influenza and fowl plague viruses, according to Andrewes.[99]

Viral Dysentery.—In 1943, Light and Hodes reported the transmission to calves of epidemic diarrhea of the newborn, a disease presumably caused by a virus. Since the agent was said to resist heating to 100 C. for five minutes, some skepticism arose as to whether a virus played a role. In a new series of experiments,[100] calves were again used; they were regularly infected with a diarrheal disease by the intranasal injection of filtered stools from sick infants. In 1 instance, the agent apparently again survived submersion in boiling water for five minutes. According to the authors, the evidence that the agent causing the disease in calves actually came from the infants was not convincing but results of control tests and neutralizing tests favored the theory.

On the basis of information that DDT (2,2-bis[p-chlorophenyl]-1,1,1-trichloroethane) may cause enteritis and symptoms of infection of the respiratory tract, Biskind [101] suggests that in many instances DDT may be the cause of epidemics of supposed viral dysentery. The suggestion seems fanciful.

Foot and Mouth Disease.—A group of workers in England, where experiments on this disease can be performed, report the results of eight years of work on Mexican foot and mouth disease in series of six papers.[102] They point out how difficult it is to secure information on the origin of an epizootic. Thirteen samples of virus were isolated, but their invasiveness was low and immunologic differences occurred among them. Species adaptation occurs; for example, a porcine strain is relatively less virulent for cattle. Deer, goats, porcupines, tapirs and other animals could be infected, but horses and donkeys could not. Of 48

97a. Ingalls, W. L., and Mahoney, A.: Isolation of Virus of Newcastle Disease from Human Beings, Am. J. Pub. Health **39**:737-740 (June) 1949.

98. Kilham, L.: A Newcastle Disease Virus (NDV) Hemolysin, Proc. Soc. Exper. Biol. & Med. **71**:63-66 (May) 1949.

99. Andrewes, C. H.: Prophylaxis of Virus Infections with Special Reference to the Use of Vaccines, Brit. M. J. **11**:1007-1009 (Dec. 11) 1948.

100. Light, J. S., and Hodes, H. L.: Isolation from Cases of Infantile Diarrhea of a Filtrable Agent Causing Diarrhea in Calves, J. Exper. Med. **90**:113-135 (Aug.) 1949.

101. Biskind, M. S.: DDT Poisoning and the Elusive "Virus X": A New Cause for Gastro-Enteritis, Am. J. Digest. Dis. **16**:79-84 (March) 1949.

102. Galloway, I. A.; Henderson, W. M., and Brooksby, J. B.: Strains of the Virus of Foot-and-Mouth Disease Recovered from Outbreaks in Mexico (pt. 1 to 6), Proc. Soc. Exper. Biol. & Med. **69**:57-84 (October) 1948.

cattle exposed to contact infection, 20 failed to show clinical evidence of disease. Seventeen of the 20 were subsequently immune to inoculation, indicating that inapparent infection had been caused. If vaccine is used it should be prepared from strains derived locally.

Viral Hepatitis.—According to Stokes and his co-workers, gamma globulin injected intramuscularly confers protection not only against infectious hepatitis but also to some extent against serum hepatitis.[103] In tests on man, gamma globulin did not alter the incidence of serum hepatitis but did prolong the incubation period. Not all batches of gamma globulin contain protective bodies, or if they do the bodies are not specific for the strain of virus dealt with.

After Oliphant succeeded in sterilizing icterogenic serum by exposure to ultraviolet rays, practical methods were devised to render serums free from the virus or, at least, to inactivate the virus.[104] Irradiated serum is available commercially.

The subject of viral hepatitis is reviewed by Havens.[105]

Amicrobic Pyuria.—Infection of the urinary tract in some instances is apparently not caused by bacteria and is mistaken for tuberculosis. A virus is suspected as the cause but the success of arsenotherapy in controlling the disease does not favor the idea. Experimental attempts to convey the infection to 4 volunteers were unsuccessful.[106]

DISEASES CAUSED BY COCCI

By Pneumococcus.—In one of the few studies made in recent years on the distribution of types of pneumococci in pneumonia, Ordman found types II, I, VII, XIV and XVII to predominate in the order mentioned.[107] The incidence of pneumococcic pneumonia has increased in South African gold mines since 1939, probably owing to the continuous importation of native laborers from tropical areas.

By Streptococcus.—In a report of a controlled study on the therapy of pharyngitis caused by hemolytic streptococci, Loge and Kilbourne[108]

103. Stokes, J., Jr.; Blanchard, M.; Neefe, J. R.; Gellis, S. S., and Wade, G. R.: Methods of Protection Against Homologous Serum Hepatitis: I. Studies on the Protective Value of Gamma Globulin in Homologous Serum Hepatitis SH Virus, J. A. M. A. **138**:336-341 (Oct. 2) 1948. Blanchard, M. C.; Stokes, J., Jr.; Hampil, B.; Wade, G. R., and Spizizen, J.: II. The Inactivation of Hepatitis Virus SH with Ultraviolet Rays, ibid. **131**:341-343 (Oct. 2) 1948.

104. Inactivation of Hepatitis Virus with Ultraviolet Rays, editorial J. A. M. A. **140**:1158-1159 (Aug. 6) 1949.

105. Havens, W. P.: Infectious Hepatitis, Medicine **27**:279-326 (Sept.) 1948.

106. Landes, R. R., and Kinnaird, R.: Amicrobic Pyuria, Mil. Surgeon **105**: 1-4 (July) 1949.

107. Ordman, D.: The Incidence and Control of Pneumonia in the Native Labourers of the Witwatersrand Goldfields, Proc. Transvaal Mine M. Officers' A. **28**:75-83 (March) 1949.

108. Loge, J. P., and Kilbourne, E. D.: Penicillin Treatment of Streptococcal Pharyngitis, Ann. Int. Med. **33**:698-714 (Oct.) 1948.

show that although penicillin shortens the duration of fever it has no significant influence on the symptoms. Penicillin therapy interferes with the antibody response, probably by quickly reducing the number of streptococci present. Whether such interference is beneficial or harmful is uncertain. Whereas penicillin therapy seemed to reduce the incidence of pyogenic complications, one still wonders whether patients with sore throat should be given penicillin therapy routinely, since the incidence of complications is so low. Furthermore, as many others have shown, in the majority of cases of sore throat hemolytic streptococci are not the cause of the disease. Diagnosis is certain only if hemolytic streptococci are present and if immunologic evidence of their invasion can be demonstrated.

Rantz and his co-workers [109] demonstrated the regular occurrence of an increase in antistreptolysin O after sore throat caused by group A hemolytic streptococci, the peak being reached about the fourth week. The degree of response varied from patient to patient, but there was no relationship between the initial titer and the nature of the acute suppurative phase of the infection. There was, however, an exaggerated immunologic response in patients in whom nonsuppurative complications, especially arthritis, later developed. These changes may be important in understanding the cause of rheumatic fever.

In another paper, Rantz and Boisvert [110] show that, so far as infections of the respiratory tract due to hemolytic streptococci were concerned, there was no relationship between the severity of the disease and the amount of fibrinolysin produced. It was suggested previously that the invasive ability of streptococci might be enhanced in proportion to the amount of streptolysin they liberated. The amount produced in vitro seemed rather to be dependent on the type of streptococcus present. As in the case of antistreptolysin O, fibrinolysin occurs in larger amounts in patients in whom poststreptococcic, suppurative or nonsuppurative sequelae develop.

Rothbard and his associates [111] tested a variety of serologic reactions to see what difference in basic pattern occurs between patients in whom rheumatic fever or purulent complications develop after they have had infection with hemolytic streptococci and those who have uneventful recovery. Of 169 patients with streptococcic infections, purulent complications developed in 29 and rheumatic fever in 38. In general, anti-

109. Rantz, L. A.; Randall, E., and Rantz, H. A.: Antistreptolysin "O": A Study of this Antibody in Health and in Hemolytic Streptococcus Respiratory Disease in Man, Am. J. Med. **5**:3-23 (July) 1948.

110. Rantz, L. A., and Boisvert, P. J.: Streptococcal Fibrinolysin (Streptokinase): A Study of This Substance and Its Antibody in Group A Hemolytic Streptococcus Sore Throat, Am. J. Med. **5**:24-32 (July) 1948.

111. Rothbard, S.; Watson, R. F.; Swift, H. F., and Wilson, A. T.: Bacteriologic and Immunologic Studies on Patients with Hemolytic Streptococcic Infections as Related to Rheumatic Fever, Arch. Int. Med. **82**:229-250 (Sept.) 1948.

streptolysin O, antifibrinolysin, anti-M precipitins and type-specific bacteriostatic antibodies developed more often in those who had rheumatic fever. But in the rheumatic group, the response of antistreptolysin O and bacteriostatic antibody was shown to be on the average lower in titer in those in whom no sequelae developed. These findings are in accord with those of others, but their significance is unknown. Apparently no single pattern of antibody response is helpful in diagnosing rheumatic fever in a given case. There was no evidence that salicylate therapy depressed the development of antibodies.

Rantz's group [112] states that, whereas vaccination subcutaneously with hemolytic streptococci gives rise to immune substances, large amounts are necessary and untoward reactions, including induced hypertensitivity, occur so often that the procedure is impractical.

Michael [113] gathered more evidence to show that, whereas tonsillectomy reduces the incidence of tonsillitis or sore throat in persons who have repeated attacks of tonsillitis, the operation has no influence in lessening the incidence of first attacks of rheumatic fever or of relapse, nor does it lower the incidence or have any beneficial influence in glomerulonephritis.

Anent tonsillectomy, Richards,[114] an otolaryngologist, said ". . . never in the history of medicine have so many physicians owed so much economic security to a single operation as to tonsillectomy." He also spoke of the old-time laryngologist who envisioned "fantastic orchards of tonsil-bearing trees."

Tillett and Sherry [115] injected a fibrin-dissolving system of streptococcic fibrinolysin (streptokinase) and desoxyribose nuclease (streptodornase) into the pleural cavity of 23 patients with various forms of exudative pleuritis. The agents cause lysis of fibrin, an alteration of fibrinogen preventing its solidification into fibrin and liquefaction of purulent exudates. Theoretically this action (*a*) may actually cause the spread of infection by destroying a protective wall, (*b*) by dissolving the wall may favor the penetration of antibiotic agents or (*c*) may prevent the formation of adhesions and scar tissue.

In a thirty year study of 1,042 children with rheumatic fever observed in a clinic, somewhat different statistical data were obtained from those

112. Rantz, L. A.; Randall, E., and Rantz, H. H.: Immunization of Human Beings with Group A Hemolytic Streptococci, Am. J. Med. **6**:424-431 (April) 1949.

113. Michael, M.: The Role of Tonsillectomy in the Management of Recurrent Streptococcal Sore Throat, Rheumatic Fever and Glomerulonephritis, Am. J. Med. **6**:462-469 (April) 1949.

114. Richards, L. G.: The Dilemma of Otolaryngology, Pennsylvania M. J. **52**:1177-1181 (Aug.) 1949.

115. Tillett, W. S., and Sherry, S.: Effect in Patients of Streptococcal Fibrinolysin (Streptokinase) and Streptococcal Desoxyribonuclease on Fibrinous, Purulent and Sanguinous Pleural Exudations, J. Clin. Investigation **28**:173-190 (Jan.) 1949.

for groups drawn chiefly from hospital wards.[116] The mean age at onset was 6.5 years. At the termination of the study 25 per cent were between the ages of 1 and 15 years and 75 per cent were from 16 to 42. Of 226 deaths, 76 per cent were caused by heart disease and 10 per cent by subacute bacterial endocarditis. The incidence of subacute bacterial endocarditis was about 2 per cent. Carditis alone occurred in 7 per cent, polyarthritis in 58 per cent and arthralgia in 10 per cent. Active carditis was demonstrable in 45 per cent, but some cardiac involvement was demonstrable in every patient. Valvular lesions and cardiac hypertrophy were noted in about one-half the patients and atrial fibrillation in 4 per cent. Cardiac involvement was present in every patient at last observation, but signs of valvular defects had regressed in one third of the group. In older studies by other workers about 25 per cent of patients escaped permanent injury to the heart. The over-all death rate was 14.7 per thousand patients per year; the highest rate occurred between the ages of 1 to 4 and 10 to 14 years. The mortality rate in this study fails to indicate any improvement resulting from better care during the past twenty years, which is at variance with a statement in the second paragraph of this review. An affected child has 4 chances out of 5 to survive fifteen years and 2 chances out of 3 to survive thirty years after the onset.

Several studies were made on agents which either interfere with the antigen-antibody reaction or inhibit the spreading effect of hyaluronidase. Acetylsalicylic acid was shown to prevent anaphylactic shock in sensitized guinea pigs, probably by interfering with the antigen-antibody reactions.[117] Sodium gentisate, the biologic oxidation product of sodium salicylate but far more active in inhibiting hyaluronidase, gave results as satisfactory as, if not better than, sodium salicylate in the treatment of rheumatic patients.[118]

Two reviews of studies on the etiology of rheumatic fever were published.[119] One contains seven hundred and seven references to papers on the subject.

Rheumatoid Arthritis.—Because patients with rheumatoid arthritis are relieved of their symptoms more frequently during pregnancy or during jaundice from various causes than as a result of any therapy thus

116. Wilson, M. G., and Lubschez, R.: Longevity in Rheumatic Fever Based on the Experience of 1,042 Children Observed over a Period of Thirty Years, J. A. M. A. **138**:794-798 (Nov. 13) 1948.

117. Campbell, B.: Inhibition of Anaphylactic Shock by Acetylsalicylic Acid, Science **108**:478-479 (Oct. 29) 1948.

118. Meyer, K., and Ragan, C.: The Antirheumatic Effect of Sodium Gentisate, Science **108**:281 (Sept. 10) 1948.

119. Swift, H. R.: The Etiology of Rheumatic Fever, Ann. Int. Med. **31**:715-738 (Nov.) 1949. Waksman, B. H.: The Etiology of Rheumatic Fever: A Review of Theories and Evidence, Medicine **28**:143-200 (May) 1949.

far tried, Hench, Kendall and their co-workers [120] state that they believe the disease to be a metabolic disorder rather than caused by infection. Many others have suspected for years that despite fever, leukocytosis, hyperglobulinemia and the presence of agglutinins for various bacteria, rheumatoid arthritis is not an infectious disease. With this in mind, the experimental administration of hormones of the adrenal cortex and the pituitary gland to patients caused striking improvement. If these observations are confirmed, rheumatoid arthritis does not belong in a discussion of infectious diseases. In retrospect one may wonder at the enormous expense and effort exerted in the past in attempts to incriminate streptococci in particular as the cause, at the multitude of blood cultures, the tests performed, the studies of nodules, the unwarranted use of vaccines supposedly specific or otherwise, and the tragedy of the millions of teeth and tonsils removed in futile attempts to control the disease by removing supposed foci of infection.

If rheumatoid arthritis is a metabolic disease, it is difficult to account for the frequency with which the serum from patients in the acute phase agglutinates sheep red cells sensitized with specific amboceptor. The reaction appears to be consistent enough to serve as a diagnostic aid. The reaction was discovered by Rose and his associates and has been partially confirmed by others.[121]

Studies by British investigators [122] failed to confirm the views of Rich and Gregory that lesions similar to those of periarteritis nodosa could be produced in rabbits by the injection of horse serum. American experimenters [123] using the same method also failed to cause lesions resembling those of rheumatic fever No Aschoff-like lesions were found in their animals; inflammatory lesions were present in 8 per cent of the control rabbits, which was similar to the observations Swift and Miller made many years ago. In regard to arthritis, only 6 of 53 inoculated rabbits had inflammatory changes of the knee joints, an incidence insufficient to establish a causal relationship to the injection of a foreign protein.

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120. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis; Preliminary Report, Proc. Staff. Meet., Mayo Clin. **24**:181-197 (April 13) 1949.

121. Jawetz, E., and Hook, E. V.: Differential Sheep Cell Agglutination Test in Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **70**:650-653 (April) 1949.

122. Alston, J. M.; Cheng, K. K., and Short, R. H. D.: Unsuccessful Attempts to Produce Periarteritis Nodosa Experimentally, J. Path. & Bact. **59**:490-492, 1947.

123. Moore, R. H., and McLean, C. R.: Lesions of Hypersensitivity Induced in Rabbits by Massive Injections of Horse Serum, Am. J. Path. **25**:413-447 (May) 1949.

124. Footnote deleted on proof.

DISEASES CAUSED BY BACILLI

Tuberculosis.—While the incidence and death rate of tuberculosis has been declining, the mortality rate in persons over 45 years old has actually increased.[125] In 1900, 24 per cent of deaths from tuberculosis were reported in persons over 45; in 1947, 52 per cent of those who died from tuberculosis were over this age. Thus thought must be given to tuberculosis at this period of life, when clinical evidence of infection may be minimal or absent. Indeed, as Medlar and his co-workers[126] have shown, since the disease is not expected in older persons the diagnosis is often missed. For example, an incorrect diagnosis of tuberculosis was made six times more often for older persons than for those under 30. Tuberculosis was recognized in only one fourth of patients who died from other diseases. Unsuspected tuberculosis in older persons therefore constitutes a currently disregarded seedbed for its spread to others.

A thorough search for tuberculosis in Minneapolis revealed many otherwise unrecognized cases.[127] In a roentgenographic survey to discover persons with pulmonary tuberculosis, cancer, cardiac abnormalities and other thoracic diseases, the proportion of those with tuberculosis among 1,500 suspects was huge. Of this number 648 were regarded as tuberculous, and of these 98, or 15 per cent, had active disease. Of 428 studied bacteriologically, Myco. tuberculosis was found in 97, or 19 per cent. Such studies illustrate the need for universal "case-finding" to discover the disease before irreparable damage occurs and to check its spread to others.

According to Pottenger,[128] the usual methods of detecting tubercle bacilli in sputum are crude and many patients regarded as "cured" actually shed bacilli. By special methods, bacilli were detected in about 95 per cent of patients discharged as "cured" from a sanatorium. Patients with chronic destructive lesions probably never stop excreting bacilli. These observations emphasize the danger of allowing supposedly cured patients to mingle with others and to spread the infection.

By using an apparatus for delivering controlled number of Myco. tuberculosis in inhaled air, Lurie and Abramson[129] were able to cause pulmonary tuberculosis akin to human pulmonary tuberculosis in the lungs of partially immunized rabbits.

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125. Anderson, R. J.: Tuberculosis Mortality in Older Age Groups, editorial, Pub. Health Rep. **64**:403-404 (April 1) 1949.

126. Medlar, E. M.; Spain, D. M., and Holliday, R. W.: Disregarded Seedbed of the Tubercle Bacillus, Arch. Int. Med. **81**:501-517 (April) 1948.

127. Roemmich, W.; Weber, F. J.; Hill, F. J., and Amos, L.: Preliminary Report on a Community-Wide Chest X-Ray Survey at Minneapolis, Minnesota, Pub. Health Rep. **63**:1285-1290 (Oct. 1) 1948.

128. Pottenger, F. M.: Public Health Significance of Rare Tubercle Bacilli in Sputum, Am. Rev. Tuberc. **58**:314-321 (Sept.) 1948.

129. Lurie, M. B., and Abramson, S.: Reproduction of Human Ulcerative Pulmonary Tuberculosis in Rabbits by Quantitative Natural Airborne Contagion, Proc. Soc. Exper. Biol. & Med. **69**:531-537 (Dec.) 1948.

Riggins and Hinshaw [130] summarized the results of the treatment with streptomycin of over 300 patients with pulmonary tuberculosis. The conclusions are about the same as those previously reached. The drug is more effective against early and subacute lesions and chronic types of cavernous or fibrous lesions than against confluent and liquefying lesions. Significant improvement, however, does occur at times in chronic disease after treatment, particularly when streptomycin is given in short courses to combat recurrent acute episodes. Drug fastness remains a serious obstacle. The failure to close cavities or to eliminate tubercle bacilli from the sputum and the frequent relapse of the disease emphasize that streptomycin alone often does not suffice for cure. Collapse therapy is often needed.

Striking success is reported with streptomycin in the treatment of 33 patients with active pulmonary tuberculosis and tuberculous enteritis.[131] All manifestations of the intestinal infection were improved. The daily dose varied from 1 to 2 Gm. intramuscularly. The course was completed in sixty to one hundred and twenty days in most instances.

A strain of tubercle bacilli whose growth actually was enhanced by streptomycin was recovered from the sputum of a patient who had been treated for ninety-six days with streptomycin.[132] The patient became worse during therapy. The danger of infection of persons with streptomycin-resistant tubercle bacilli is growing. Two such instances are reported.[133]

Evidence suggests that resistance of tubercle bacilli to streptomycin occurs less often in patients treated with a combination of streptomycin, paraaminosalicylic acid and promin® (sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate) than in patients treated with streptomycin alone.[134]

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130. Riggins, H. M., and Hinshaw, H. C.: Streptomycin-Tuberculosis Research Project of the American Trudeau Society: A Summary Report, Am. Rev. Tuberc. **59**:140-167 (Feb.) 1949.

131. Mason, E. F.; Kridelbaugh, W. W.; Crouch, W. H., and Ward, M.: Streptomycin in the Treatment of Tuberculous Enteritis: A Report of Thirty-Three Cases, Am. J. M. Sc. **217**:28-46 (Jan.) 1949.

132. Spendlove, G. A.; Cummings, M. M.; Fackler, W. B., Jr., and Michael, M., Jr.: Enhancement of Growth of a Strain of M. Tuberculosis (Var. Hominis) by Streptomycin, Pub. Health Rep. **63**:1177-1179 (Sept. 3) 1948.

133. Furtos, N. C., and Doane, E. A.: Transmission of Streptomycin-Resistant Tubercle Bacilli in Man, J. A. M. A. **140**:1274-1275 (Aug. 20) 1949. Brennan, A. J., and Wichelhausen, R. H.: Streptomycin-Resistant Tubercle Bacilli: Isolation of Resistant Organisms from Pleural Fluid Prior to Institution of Streptomycin Therapy, ibid. **140**:1275 (Aug. 30) 1949.

134. Karlson, A. G.; Pfuetze, K. H.; Carr, D. T.; Feldman, W. H., and Hinshaw, H. C.: The Effect of Combined Therapy with Streptomycin, Para-Aminosalicylic Acid and Promin on the Emergence of Streptomycin-Resistant Strains of Tubercle Bacilli: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**:85-88 (Feb. 16) 1949.

On the basis of the unproved idea that potassium iodide dissolves tubercles and liberates tubercle bacilli, tuberculous guinea pigs were treated with streptomycin alone and with a combination of potassium iodide and streptomycin.[135] At the end of the test, 5 of 10 animals treated with the antibiotic drug alone showed mild spread of tuberculosis whereas no tubercles were seen in animals receiving the combined agents.

Leprosy.—An editorial [136] comments on the persistence of the baleful Biblical attitude toward the isolation of lepers. Leprosy actually is less contagious than tuberculosis, and more humane methods of management are desirable. Even the name leper might well be replaced with some other term, but one questions the wisdom of reversion to an eponym like Hansen's disease or, still worse, hansenosis, hansenotic or hansenide patients, as has been proposed. It is hoped that no one will suggest the names kochosis for tuberculosis, or neisserosis for gonorrhea.

Brucellosis.—It has been my impression that the striking statistical increase in the incidence of brucellosis was due to increased awareness of the disease and to the improved methods of diagnosis and reporting of cases. Studies by Magoffin and his co-workers,[137] however, indicate an actual sharp increase in the number of both human and bovine infections in Minnesota during the past ten years. The studies also show how different varieties of brucella predominate in human infections in certain areas, depending on the general occupation. In Iowa, for example, where the swine industry is extensive, most of the isolated strains are Brucella suis; in Minnesota, Wisconsin and Michigan, with a large dairy industry, Brucella abortus is most commonly encountered. Nearly three fourths of the Minnesota patients had contact with farm animals; ingestion of raw milk accounted for the disease in the rest. The agglutination test is said to be highly reliable in diagnosis.

The treatment of brucellosis has passed through many phases, most of them unsuccessful. After a number of different antiseptics, vaccines, nonspecific protein shock therapy and antiserums had been tested, new hope arose when the sulfonamides were introduced. These too proved to be of no value, as did penicillin. Streptomycin was promising for a time but eventually disappointing, and soon a combination of streptomycin and sulfadiazine met the same fate. Aureomycin next captured the imagination, but even this agent often has failed.[138]

135. Woody, E., and Avery, R. C.: The Combined Effect of Potassium Iodide and Streptomycin on Established Tuberculosis in Guinea Pigs, Science **108**:501-505 (Nov. 5) 1948.

136. New Developments in the Management of Leprosy, editorial, Ann. Int. Med. **30**:692-700 (March) 1949.

137. Magoffin, R. L.; Kabler, P.; Spink, W., and Fleming, D.: An Epidemiologic Study of Brucellosis in Minnesota, Pub. Health Rep. **64**:1021-1043 (Aug. 19) 1949.

138. Culbertson, J. T.: Symposium on Brucellosis, September 22-23, 1949, Science, **110**:469 and 485 (Nov. 4) 1949. Eisele, C. W., and McCollough, N. B.: The Treatment of Brucellosis, Illinois M. J. **96**:241-244 (Oct.) 1949.

An Argentine physician [139] found evidence of lesions of the cardiovascular system in 55 of 428 patients with brucellosis. Myocardial involvement is commoner than endocarditis or pericarditis.

McVay and his co-workers [140] add further information concerning the presence of Brucella in apparently healthy people, as has been noted previously by others. Brucella was cultivated from 3 of 34 prostate glands and from 1 of 43 fallopian tubes removed at operation. No agglutinin for Brucella was present in any of the serums, but the skin tests were strongly positive in those who harbored the bacilli.

Morales-Otero and González [141] offer a new, readily soluble form of purified brucella protein which lends itself conveniently to intradermal tests.

Diphtheria.—This disease, according to Fisher and Cobb,[142] has increased in incidence in the past few years. There is a dangerous tendency on the part of many physicians to regard diphtheria as a disease easily controlled by immunization with toxoid. Diphtheria is not confined to children, and previously immunized persons may contract it. Twelve of 30 patients with the severe form of diphtheria had been "immunized." The virulence test is often inaccurate, as six of the strains involved were classed as avirulent. Since prompt and energetic treatment with antitoxin is of such great value, it is necessary to consider diphtheria in patients suspected of having acute tonsillitis and pharyngitis, so-called Vincent's infection, infectious mononucleosis or croup.

Pertussis.—Toomey [143] collected reports on 38 cases of serious untoward reactions in the central nervous system to pertussis vaccine, an agent previously regarded as innocuous. The reaction may be allergic in nature, as in the case of antirabies vaccination. No child who has had disease of the central nervous system, convulsions or a history of convulsions in its family should be given large doses of vaccine.

Typhoid.—In one of the longest studies ever made on "typhoid carriers"—it lasted twenty-eight years—two Norwegians [144] followed the

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139. Maldonado-Allende, I.: Clinical Aspects of Cardiovascular Brucellosis, Prensa méd. argent. **35**:2323-2325 (Dec. 3) 1948.

140. McVay, L. V.; Guthrie, F.; Michelson, I. D., and Sprunt, D. H.: Isolation of Brucella from Apparently Healthy Individuals, Proc. Soc. Exper. Biol. & Med. **69**:507-608 (Dec.) 1948.

141. Morales-Otero, P., and González, L. M.: Readily Soluble Form of P. B. P. for Use as a Routine Diagnostic Test, Proc. Soc. Exper. Biol. & Med. **71**:387-388 (July) 1949.

142. Fisher, A. M., and Cobb, S.: The Clinical Manifestations of the Severe Form of Diphtheria, Bull. Johns Hopkins Hosp. **83**:297-325 (Oct.) 1948.

143. Toomey, J. A.: Reactions to Pertussis Vaccine, J. A. M. A. **139**:448-449 (Feb. 12) 1949.

144. Vogelsang, T. M., and Bøe, J.: Temporary and Chronic Carriers of Salmonella Typhi and Salmonella Paratyphi B., J. Hyg. **46**:252-261 (Sept.) 1948.

course of 1,400 patients who had had typhoid or paratyphoid B. Of these about 50 per cent were temporary carriers, that is, up to three months. Carriers for more than three months rarely, if ever, became free. Of those with typhoid 3.3 per cent became chronic carriers, and of those with paratyphoid B, 1.9 per cent. Cholecystectomy is said to have failed in ridding only 1 carrier of bacilli.

Attempts to cause a rise in the amount of fecal agglutinin (coproantibody) with subcutaneous injections of antityphoid vaccine before agglutinins developed in the blood failed.[145] After vaccination it would be most unlikely for antibody to appear in the feces before it appears in the serum.

The value of chloramphenicol in the treatment of typhoid has been discussed previously in this paper.

A report has been made of the appearance of an avirulent strain of Salmonella typhosa 58, which is used for the routine production of antityphoid vaccine.[146] Ordinarily the virulent phase forms of this bacterium had been repeatedly isolated from a carrier. On this occasion the avirulent strain was similar in all respects to the usual one except that it was not pathogenic for mice. Subsequent "isolates" were virulent as usual.

Dienes[147] succeeded in isolating and propagating minute colonies of the L type of organism from typhoid bacilli on serum agar containing penicillin.

Cholera.—A study of 687 patients with cholera treated during the Shanghai epidemic of 1946 is reported.[148] As in the epidemic I observed at Chungking the year before, the mortality rate was reduced to 4.7 per cent by prompt and thorough rehydration. While the administration of sulfadiazine appeared to shorten the disease, it can in no way replace the copious infusion of salt water. Castellani[149] writes that all patients treated with basic fuchsin recovered. The work, to say the least, needs confirmation.

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145. Goodlow, R. J.; Rittenberg, S. C., and Silliker, J. H.: Coproantibody Response in Humans Following TAB Vaccination, Proc. Soc. Exper. Biol. & Med. **70**:543-545 (March) 1949.

146. Batson, H. C.; Landy, M., and Abrams, A.: Avirulent Isolate of Salmonella Typhosa 58 (Panama Carrier), Pub. Health Rep. **64**:671-674 (May 27) 1949.

147. Dienes, L.: Isolation of L Type Colonies from Typhoid Bacilli with the Aid of Penicillin, Proc. Soc. Exper. Biol. & Med. **68**:589-590 (July-Aug.) 1948.

148. Tao, S. C.; Woo, M. O., and Loh, W. P.: Clinical Observations on Six Hundred and Eighty-Seven Cases of Cholera, Chinese M. J. **66**:377-388 (July) 1948.

149. Castellani, A.: Fuchsin in the Therapy of Cholera, Riv. dell'Inst. sieroterap. ital. **23**:73-74 (April-June) 1948.

An enigma still remains as to the relation of the so-called El Tor vibrio and cholera.[150] The El Tor vibrio is found in patients, in carriers and in the water of wells and it is sometimes present in a community where no disease occurs. The vibrio causes only slight morbidity and sporadic cases. Because of the epidemiologic and certain bacteriologic differences, it is proposed to give it a distinctive name differentiating the disease it causes from true cholera. One questions the wisdom of this suggestion. It would seem better to regard cholera as a clinical entity caused by different strains of vibrio. One would abhor the introduction of the proposed term "paracholera." Gallut, in Paris, confirmed the work of Burrows in classifying cholera vibrios on an antigenic basis.[151] The new arrangement permits dropping of the eponyms Ogawa, Inaba, etc. and also allows the preparation of better vaccines.

Recalling studies showing a probable antigenic relationship between V. comma and Brucella, as reported in last year's review, it is now evident that certain antigenic fractions of Salmonella are also present in cholera vibrios.[152]

Singer and his associates obtained filtrates from cultures of V. comma which cause shedding of the epithelium in the intestines of guinea pigs.[153] The active substance is antigenically similar to the somatic or "O" antigen of the vibrio.

Tetanus.—Diaz-Rivera and his co-workers[154] studied 59 cases of tetanus in Puerto Rico. The mortality rate was 20 per cent. The rate was 50 per cent in patients under 10 or over 50 years and 15 per cent in those between these ages, who comprised the majority of cases. The authors ascribe this low rate to thorough treatment, including the administration of antitoxin in moderate amounts and of penicillin. They conclude that tetanus antitoxin is needed to neutralize free toxin but that it is of no value in preventing convulsions or in relieving them, regardless of how large an amount is injected or how early it is given after the disease has started. Penicillin is valuable to control secondary infection.

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150. Paracholera (El Tor): Enteritis Choleriformis El Tor van Loghem, Chron. World Health Organ. **3**:61-62 (March) 1949.

151. Specific Antigen of Cholera Vibrio: Complete Analysis and Practical Application, Chron. World Health Organ. **3**:62-63 (March) 1949.

152. Felsenfeld, O.: Antigenic Relationship of Salmonella to Inaba Strains of Vibrio Comma Isolated in Egypt, Proc. Soc. Exper. Biol. & Med. **69**:95-96 (Oct.) 1948.

153. Singer, E.; Wei, S. H., and Hoa, S. H.: Immunological Studies of Cholera Filtrates, J. Immunol. **59**:341-348 (Aug.) 1948.

154. Diaz-Rivera, R. S.; Deliz, L. R., and Berio-Suarez, J.: Penicillin in Tetanus: A Clinical Analysis of Fifty-Nine Cases, J. A. M. A. **138**:191-194 (Sept. 18) 1948.

Anthrax.—Reilly and Beeson [155] describe the first reported case of the transmission of anthrax from one person to another. A patient's wife dressed his wounds, and several days later the disease developed in her. Four patients were given 300,000 units of penicillin and 6 Gm. of sulfadiazine, and 1 received 2 Gm. of streptomycin for five days. All recovered. LaBocetta [156] treated 36 patients with 100,000 to 200,000 units of penicillin daily intramuscularly. Lesions continued to spread and edema increased sometimes for thirty-six hours during treatment, but all patients recovered. Penicillin apparently has no effect on the inflammatory process.

Bacteroides.—McVay and his co-workers [157] reported 2 cases of septicemia caused by Bacteroides funduliformis, an anaerobic bacillus. Cure was obtained in patients with this usually fatal infection by treatment with aureomycin. Eighteen patients were observed in the authors' hospital during five years. The disease occurs more frequently than is usually thought.

Melioidosis.—A case of melioidosis with pain and enlargement of a cervical lymph node, without fever and with recovery after several weeks, is reported.[158] It is stated that the death rate of the disease is 95 per cent. This makes one wonder whether only the fatal cases are recognized and the milder ones missed, as was once true with histoplasmosis, coccidioidomycosis and other diseases. Recovery of the patient was ascribed to therapy with sulfapyridine. All antibiotic agents except chloramphenicol were ineffective in inhibiting the growth of Malleomyces pseudomallei (Pfeifferella whitmori).

DISEASES CAUSED BY FUNGI

Histoplasmosis.—A six year study on student nurses in different parts of the country yielded important information on histoplasmosis and tuberculosis.[159] Pulmonary infiltration and enlargement of the mediastinal lymph nodes were indicated on initial roentgenograms for 224 of about 12,000 nurses. All were tested with purified protein

155. Reilly, W. A., and Beeson, C. F.: Antibiotic Therapy for Cutaneous Anthrax: Report of Five Cases, Arch. Int. Med. **82**:529-533 (Dec.) 1948.

156. LaBocetta, A. C.: Anthrax: Thirty-Six Human Cases of External Type Treated Successfully with Penicillin, Am. J. M. Sc. **216**:407-410 (Oct.) 1948.

157. McVay, L. V.; Guthrie, F., and Sprunt, D. H.: Septicemia Due to Bacteroides: Aureomycin Hydrochloride Therapy in Two Cases Due to Bacteroides Funduliformis, J. A. M. A. **140**:1150-1152 (Aug. 6) 1949.

158. Green, R., and Mankikar, D. S.: Afebrile Cases of Melioidosis, Brit. M. J. **1**:308-310 (Feb. 19) 1949.

159. Edwards, L. B.; Lewis, I., and Palmer, C. E.: Studies of Pulmonary Findings and Antigen Sensitivity Among Student Nurses: III. Pulmonary Infiltration and Mediastinal Adenopathy Observed Among Student Nurses at the Beginning of Training, Pub. Health Rep. **63**:1569-1600 (Dec. 3) 1948.

derivative of tuberculin U. S. P. and histoplasmin. The incidence of roentgenographic changes in those who reacted to neither tuberculin nor histoplasmin was 0.26 per cent, in contrast with 3.5 per cent of those who reacted to tuberculin and 4.98 per cent of those who reacted to histoplasmin. The inference is, of course, that histoplasmosis may cause pulmonary shadows in the group studied more often than does tuberculosis. Of the 38 nurses who showed enlargement of the mediastinal lymph nodes, 31 reacted to histoplasmin. Nodular infiltration was found most frequently in histoplasmin-positive reactors; the shadows were usually scattered throughout the lung fields, rather than limited to the upper portions as in those who reacted to tuberculin. Evidence of the so-called primary complex of tuberculosis was found in 17 nurses. Of these, 14 reacted to histoplasmin alone, and 3, to both histoplasmin and tuberculin. No evidence of active histoplasmosis was observed, but new lesions, presumably tuberculous, developed in 7 tuberculin-positive nurses.

The studies strongly support, but do not prove, the role of histoplasmosis in causing abnormal roentgenographic pulmonary shadows, especially in otherwise healthy persons. The fourth paper of this series of studies by the same investigative team [160] is based on observations on 16,320 persons in ten widely scattered centers of the United States, and the results confirm those of previous studies. Calcification among reactors to histoplasmin alone was three times as high as among reactors to tuberculin alone, and much more calcification was associated with sensitivity to histoplasmin than with sensitivity to tuberculin. The results suggest that tuberculosis, plus whatever causes sensitivity to histoplasmin (ostensibly histoplasmosis), accounts for nearly all the detected pulmonary calcification in the persons studied. Beadenkopf and his co-workers [161] in Chicago obtained similar information from a study of 6,000 students who came from various parts of the country.

Histoplasmin elicits positive reactions in about 75 per cent of persons in Kansas, but during critical illness of any kind the percentage is much lower.[162] In about half the patients who recover, the reaction

160. Goddard, J. C.; Edwards, L. B., and Palmer, C. E.: Studies of Pulmonary Findings and Antigen Sensitivity Among Student Nurses: IV. Relationship of Pulmonary Calcification with Sensitivity to Tuberculin and to Histoplasmin, Pub. Health Rep. **64**:820-844 (July 1) 1949.

161. Beadenkopf, W. G.; Loosli, C. G.; Lock, H.; Rice, F. A., and Slattery, R. V.: Tuberculin, Coccidioidin, and Histoplasmin Sensitivity, in Relation to Pulmonary Calcification: A Survey Among Six Thousand Students of the University of Chicago, Pub. Health Rep. **64**:17-30 (Jan. 7) 1949.

162. Furcolow, M. L.; Enge, M. E., and Bunnell, I. L.: Depression of Tuberculin and Histoplasmin Sensitivity Associated with Critical Illness, Pub. Health Rep. **63**:1296-1298 (Oct. 1) 1948.

again becomes positive. The same changes occur in the tuberculin reaction. The suppression of the reaction is presumably nonspecific.

Price and I [163] believe that progress in the knowledge of histoplasmosis was impeded until several early errors of opinion were rectified and certain points established: that histoplasmosis is a fungus disease; that it resembles tuberculosis more than kala-azar, and that many more mild cases than fatal exist. Evidence was presented in the case of a patient observed by us and in 1 studied by Israel and DeLamater that histoplasmosis and sarcoidosis may be indistinguishable clinically and pathologically unless Histoplasma capsulatum is isolated and identified. In these patients both sarcoidosis and histoplasmosis may have been present, but H. capsulatum may cause disease regarded at times as sarcoidosis. Others [164] point out a possible relationship between histoplasmosis and lymphoblastoma, but perhaps lymphoblastoma provides circumstances favorable to the invasion by the fungus.

In experimental studies,[165] lesions developed in the liver and spleen in animals infected with H. capsulatum by the oral route, and intranasal inoculation of animals caused pulmonary lesions.

Further studies of the complement fixation reaction reveal that a high titer is often present in the early acute phase of the disease and is transitory.[166] The titer in patients with chronic histoplasmosis is not much different from that in persons without the disease. Humoral antibodies were present in 10 of 73 histoplasmin-positive persons and in 6 of 134 histoplasmin-negative ones. Unfortunately, there is some cross reaction with the antigens of Blastomyces, in particular Blastomyces dermatitidis. The application of the skin test with histoplasmin did not affect the titer.

An important missing link in the epidemiology of histoplasmosis was furnished by Emmons' discovery [167] of the presence of H. capsulatum in 2 of 387 samples of soil collected on a farm where rats were found to have histoplasmosis. The epidemiologic analogy with Coccidiodes immitis is striking. Skin tests with histoplasmin indicate that cattle may be infected with H. capsulatum.[167a]

163. Reimann, H. A., and Price, A. H.: Histoplasmosis in Pennsylvania: Confusion with Sarcoidosis and Experimental Therapy with Bacillomycin, Pennsylvania M. J. **52**:367-371 (Jan.) 1949.

164. Cawley, E. P., and Curtis, A. C.: Histoplasmosis and Lymphoblastoma: Are These Diseases Related? J. Invest. Dermat. **11**:443-453 (Dec.) 1948.

165. Allen, R. M.: Experimental Histoplasmosis: Portal of Entry of the Fungus, Am. J. Trop. Med. **28**:857-861 (Nov.) 1948.

166. Campbell, C. C., and Saslaw, S.: Use of Yeast Phase Antigens in a Complement Fixation Test for Histoplasmosis, Pub. Health Rep. **64**:551-560 (May 6) 1949.

167. Emmons, C. W.: Isolation of Histoplasma Capsulatum from Soil, Pub. Health Rep. **64**:885-896 (July 15) 1949.

167a. Furcolow, M. L., and Ruhe, J. S.: Histoplasmin Sensitivity Among Cattle, Am. J. Pub. Health **39**:719-721 (June) 1949.

Coccidioidomycosis.—The gravity of coccidioidomycosis during pregnancy is pointed out by Smale and Birsner,[168] who reported a fatal outcome in 4 women, 3 of whom were Negroes; 3 had meningitis. Healthy infants were delivered in 3 instances.

Nocardiosis.—A patient was suspected of having pulmonary tuberculosis and treated as such for two years, but on only one occasion were bacilli thought to be Myco. tuberculosis found in the sputum.[169] Pleural effusion then developed, and Nocardia asteroides was cultivated from the fluid. Penicillin and streptomycin had no effect. After sulfadiazine therapy was started, Nocardia could still be recovered, but with more difficulty, for as long as thirty-eight days. Recovery occurred, however. The patient received a total of 75 Gm. of sulfadiazine intrapleurally and 1,268 Gm. (2.8 pounds) orally over a five month period. The authors state the belief that sulfadiazine is the drug of choice for treatment.

In another instance,[170] N. asteroides caused pulmonary disease and empyema. Cure was apparently brought about by surgical drainage combined with the administration of sulfadiazine, penicillin and streptomycin.

In a third reported case [171] there was chronic granulomatous disease with enlargement of the abdomen and malnutrition but no fever; the disease was presumably caused by a hitherto undescribed form of Nocardia. The reticuloendothelial system was chiefly affected. The agent was found intracellularly. One cannot be certain whether Nocardia actually caused the disease or whether it grew as a saprophyte in tissue injured by some malignant lymphoma.

Weed and Baggenstoss [172] studied 35 fatal cases in which the condition was diagnosed as actinomycosis. Actinomyces bovis could be demonstrated positively in only 21 patients at necropsy. In 1 of the others Nocardia was found, and in 13 of the 21 the infection was mixed. "Sulfur granules" may be produced by micro-organisms other than A. bovis. Differentiation of infection with Nocardia from that with

168. Smale, L. E., and Birsner, J. W.: Maternal Deaths from Coccidioidomycosis, J. A. M. A. **140**:1152-1154 (Aug. 6) 1949.

169. Glover, R. P.; Herrell, W. E.; Heilman, F. R., and Pfuetze, K. H.: Nocardiosis: Nocardia Asteroides Infection Simulating Pulmonary Tuberculosis, J. A. M. A. **136**:172-175 (Jan. 17) 1948.

170. Hager, H. F.; Migliacco, A. V., and Young, R. M.: Nocardiosis: Pneumonia and Empyema Due to Nocardia Asteroides, New England J. Med. **241**: 226-231 (Aug. 11) 1949.

171. Cuttino, J. T., and McCabe, A. M.: Pure Granulomatous Nocardiosis: A New Fungus Disease Distinguished by Intracellular Parasitism, Am. J. Path. **25**:1-10, 1949.

172. Weed, L. A., and Baggenstoss, A. H.: Actinomycosis: Pathologic and Bacteriologic Study of Twenty-One Fatal Cases, Am. J. Clin. Path. **19**:201-216 (March) 1949.

Actinomyces should always be made; the former grows aerobically and is sensitive to sulfonamides, the latter grows anaerobically and is sensitive to penicillin.

Q FEVER

Nearly 300 patients with Q fever and 3 deaths were observed from September 1947 to July 1948 in the Los Angeles area, during all seasons of the year.[173] Many more undetected instances probably occurred. Q fever no doubt was present in the community long before but was not recognized or was mistaken for viral pneumonia or influenza. Diagnosis was made in recent cases by a rising complement-fixing antibody titer or by recovering Coxiella burnetii from the tissues, blood or urine. The clinical symptoms and variations in the severity of the disease are like those of viral pneumonia. Roentgenographic evidence of involvement of the lungs was found in 97 of 115 patients. There were more dairymen and housewives affected than any other group of persons. Three likely sources for the spread of Q fever are the following: (*a*) occupation in dairy or livestock industries; (*b*) residence near a dump or livestock yards, and (*c*) household use of raw milk. In half the cases none of these suggestions was tenable. The source of the epidemic in Haifa, Israel,[174] was as obscure as that in Los Angeles. The outbreak began in winter; no contact with cattle was obvious, but dust from straw was suspected. The first reported case of Q fever in Philadelphia occurred in a wool-processing plant.[175] The coxiellas were believed to exist in raw wool and goat hair and to have been inhaled as dust. Of 187 employees 37 had an undiagnosed disease, but the complement fixation reaction reached a high titer in 29 of these.

Other studies suggest that the infection may be transmitted by contaminated clothing to laundry workers.[176] Animals were infected experimentally by inhalation of infected dust.[177] Houseflies may carry the infection, but mosquitoes of the species Aedes aegypti apparently do not. Sheep and goats are known to harbor the disease. Aureomycin is of value in treatment.[178]

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173. Beck, M. D.; Bell, J. A.; Shaw, E. W., and Huebner, R. J.: Q Fever Studies in Southern California: II. An Epidemiological Study of Three Hundred Cases, Pub. Health Rep. **64**:41-56 (Jan. 14) 1949.

174. The First Diagnosed Outbreak of Q Fever in Israel, Foreign Letters, Israel. J. A. M. A. **140**:1111 (July 30) 1949.

175. Janton, H., and Sigel, M. M.: Q Fever in a Wool Processing Plant. Abstracted, Tr. & Stud. Coll. Physicians, Philadelphia, **17**:73-74 (June) 1949.

176. Oliphant, J. W., and others: Q Fever in Laundry Workers, Presumably Transmitted from Contaminated Clothing, Am. J. Hyg. **49**:76-82 (Jan.) 1949.

177. Philip, C. B.: Observations on Experimental Q Fever, J. Parasitol. **34**: 457-464 (Dec.) 1948.

178. Lennette, E. H.; Meiklejohn, G., and Thelen, H. M.: Treatment of Q Fever in Man with Aureomycin, in conference on Aureomycin: A New Antibiotic, Section on Biology, New York Academy of Science, July 21, 1948.

The knowledge of Q fever is summarized in three papers.[179] One learns that the "Q" does not stem from Queensland, where the disease was discovered, but that it stands for "query." The disease occurs in Europe, Central America, Australia, the United States and Palestine, and no doubt will be found elsewhere when sought. The report of Huebner and his associates[179b] deals with 625 collected cases. The almost complete absence of involvement of the upper respiratory tract aids in distinguishing the disease clinically from viral pneumonias, influenza and colds, with which it is otherwise often confused. Differentiation from coccidioidomycosis and psittacosis is more difficult. Diagnosis can be made by the isolation of C. burnetii, by complement fixation tests and by specific agglutination tests on rickettsias.

MISCELLANEOUS SUBJECTS

Reiter's Disease.—In a monograph on Reiter's disease, Paronen[180] describes 344 cases in Finland from 1943 to 1946. Ninety per cent of the patients were males, and epidemic bacillary dysentery preceded the condition in 96.4 per cent of the patients. In the remainder, dysentry was probably subclinical. The author regards Reiter's disease as a sequel of bacillary dysentery and not as a viral disease or as one caused by pleuropneumonia-like bacteria. The clinical manifestations may be caused by an allergic state. Eosinophilia occurred in 33 per cent of patients.

Trichinosis.—Thorborg and his associates[181] report the first cases of trichinosis in Greenland. They describe numerous small outbreaks and suggest that many were unrecognized in the past, probably being mistaken for food poisoning. They excluded pork but incriminated meat of the seal, walrus, dog, polar bear and arctic fox as sources. Trichinosis is probably widespread in arctic regions.

Kala-Azar.—This disease developed in 3 veterans fourteen to twenty-one months after they had left endemic areas.[182] The long time which elapsed was erroneously called the "incubation period." Treatment with ethylstibamine (neostibosan®) was successful in each instance. The first 2 cases of kala-azar known to be transmitted with transfused blood

179. (*a*) Parker, R. R.; Bell, E. J., and Stoenner, H. G.: Q Fever: A Brief Survey of the Problem, Am. Vet. M. A. **114**:55-60 (Feb.) 1949. (*b*) Huebner, R. J.; Jellison, W. L., and Beck, M. D.: Q Fever — A Review of Current Knowledge, Ann. Int. Med. **30**:495-509 (March) 1949. (*c*) Dyer, R. E.: Q Fever: History and Present Status, Am. J. Pub. Health **39**:471-477 (April) 1949.

180. Paronen, I.: Reiter's Disease: Study of Three Hundred and Forty-Four Cases Observed in Finland, Acta med. Scandinav. (supp. 212) **131**:1-112, 1948.

181. Thorborg, N. B.; Tulenius, S., and Roth, H.: Trichinosis in Greenland, Acta path. (supp.) **25**:778-794, 1948.

182. Duffy, J. P., and Davison, L. E.: Kala-Azar: Three Cases Developing in Veterans, Am. J. M. Sc. **217**:21-27 (Jan.) 1949.

have been recorded.[183] The danger of transmitting Chagas' disease (American trypanosomiasis) by transfusion of blood is also pointed out.[184]

Use of Chloroquine.—Chloroquine diphosphate is as effective as emetine hydrochloride in the treatment of amebic hepatitis and amebic liver abscess and is without the disadvantage of toxicity of the latter.[185] It is no better than emetine in the treatment of intestinal amebiasis.

Toxoplasmosis.—Sabin and Feldman[186] find visual evidence to confirm the idea that intracellularly located micro-organisms are invulnerable to the effects of humoral antibodies. In the use of dyes they have a new method to differentiate between recent and old infections with Toxoplasma and to survey the incidence of the disease in animals. The test is simpler than the customarily used neutralization test and eventually may be perfected to apply to other protozoal, bacterial or viral disease. Material made from Toxoplasma and called toxoplasmin is available for a diagnostic skin test.[187]

Investigators in Holland isolated Toxoplasma from the spinal fluid of a 6 week old child with hydrocephalus.[188] Serum from the infant's mother contained specific antibodies. Evidently toxoplasmosis occurs in Holland. The first case recognized in England is described.[189] A brief summary of the 29 cases previously reported in the literature and of 20 new ones is included in a monograph on the subject by Binkhorst.[190] The subject is reviewed also by Frenkel.[191]

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Clonorchiasis.—Edelman and Springarn [192] report 4 cases of clonorchiasis in New York in white emigrants who had lived in Shanghai, where the disease probably was contracted. The symptoms were chiefly present in the upper part of the abdomen and were probably caused by hepatic, biliary or duodenal disorders; in 1 patient there was only prolonged low fever. The disease is prevalent in the Orient and must be suspected in the case of obscure illnesses in persons who have resided in endemic areas, particularly if they have eaten raw fresh-water fish.

Hodgkin's Disease.—Another attempt was made to establish the infectious origin of Hodgkin's disease.[193] Cytoplasmic inclusion bodies were seen in tissue cultures from lymph nodes of patients with the disease but not in normal lymph node tissue or in that of patients with lymphosarcoma or leukemia. Tissue cultures from lymph nodes affected by Hodgkin's disease gave evidence of cellular degeneration not seen in normal lymph node tissue. The report is reminiscent of the work of Gordon, associating elementary bodies with Hodgkin's disease, and of the suggested relationship of the disease to brucellosis. It needs confirmation.

Fever.—Divergent views persist as to the role played by bacteria or their products as causes of fever. In one study,[194] fever was thought to have been due to a pyrogenic substance obtained from Ps. aeruginosa, which when injected into curarized dogs seemed to cause a sudden and severe reduction in heat loss. The increase in the production of heat seemed to be related to the fever itself as an effect, not as a cause. It was once suggested that the muscular effort of shivering raised the temperature, but this factor played no role in these experiments. On the other hand, according to Bennett,[195] bacterial pyrogens and sterile exudates of acute inflammation both cause fever in rabbits but it is unlikely that the bacterial pyrogens play an important role. Fever is likelier to be caused by products resulting from the injury of tissue by the bacteria. Fever resulting from the injection of sterile exudates was not caused by the presence of bacterial pyrogen. Interesting observa-

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tions on parabiotic pygopagus twins indicate that substances affecting the control of temperature are disseminated by the blood.[196]

Lymphocytes.—Habel and his co-workers [197] were unable to confirm previous views concerning lymphocytes as the source of antibodies. The large amount of antibody found in the lymphocytes in experimental studies may be accounted for in part by transfer from the blood.

Diet.—In a short essay, Schneider [198] discusses the complexity of the question as to whether diet can influence natural resistance to infection. The answer he states is a small "no" and a bigger "yes." In experiments attention must be given to many variables. The author's recent results suggest that a new nutritional entity responsible for the survival of certain experimentally infected mice has been localized in wheat germ.

Keys [199] also comments on the uncertainty of the influence of undernutrition on resistance to infection. The problem, he writes, is complicated, and each infectious disease must be considered separately. Many experimental studies have led to contradictory conclusions, and clinical records both support and oppose the view that caloric deficiency predisposes to infections. It must be pointed out that pestilence during World War II never was rampant despite periods of mass starvation, especially in Greece and Holland. Diphtheria affected well fed troops as severely as the underfed population. From these actual observations it must be concluded that the old association of pestilence with famine was due more to sanitary factors than to caloric deficiency.

Tuberculosis is a different matter, since it greatly increased in incidence and mortality in certain European countries during the war. According to experiments by Koerner's group [200] on induced tuberculosis in rats, the animals which received a diet containing 40 per cent protein showed less extensive and better localized disease and yielded fewer bacilli than did those which received less.

Infection of Wounds.—By saturating the outer layer of bandages on "model wounds" with cultures of Ps. aeruginosa, Colebrook [201] demonstrated that infection of wounds may occur by penetration of pathogenic

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bacteria through soaked dressings. This can be prevented by a layer of bacteria-impervious plastic fiber inserted in the dressing.

Use of Mercury Compounds.—A controversy persists regarding the value of organomercurial agents in local infections. After the appearance of Morton's paper last year, investigators of several commercial firms questioned his conclusions that these agents are not ideal as disinfectants; but the matter is still unsettled, and in the last study by Banti [202] it is stated that "mercurial compounds appear . . . to be very poor germicides."

Control of Flies.—Watt and Lindsay [203] report a large scale attempt to reduce the number of flies by the regular application of DDT in a community in Texas. Untreated areas were used as controls. The study included observations on the possible value of control of flies on the incidence of acute diarrheal diseases. It was evident that Shigella infections were reduced in number in treated areas and that infections with the Salmonella group were also diminished. There is no doubt that the number of flies can be reduced greatly, but soon after the effect of the insecticide wears off they return in the usual numbers. A more basic method of control is to eliminate man-made breeding places by good civic housekeeping. It is disconcerting to learn of the development of resistance of houseflies to DDT.[204]

Fleabites.—Common rat fleas may become infected with Salmonella enteritidis when feeding on infected mice and may then infect other mice by biting them.[205] The feces of fleas also contain the bacteria and may serve as another mode of conveyance. Fleabites apparently may transmit Salmonella to man, according to this evidence.

Disinfection of Air.—The effectiveness of ultraviolet radiation in the sterilization of air is seriously questioned.[206] In a six year study on 400 inmates of an institution, dormitories were irradiated with more than the amount of ultraviolet rays usually recommended. In spite of this, there was no consistent reduction in mild air-borne infections of the respiratory tract or in the number of bacteria in the air as compared with control rooms not irradiated.

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News and Comment

GENERAL NEWS

National Conference on Cardiovascular Diseases.—A National Conference on Cardiovascular Diseases will be held January 18 through January 20, 1950, at the Mayflower Hotel, Washington, D. C. The conference is sponsored jointly by the National Heart Institute and the American Heart Association. Dr. C. J. Van Slyke, Director of the Institute, and Dr. H. M. Marvin, president of the American Heart Association, are its co-chairmen.

Dr. Paul D. White, former president of the American Heart Association and now Chief Medical Advisor to the National Heart Institute of the United States Public Health Service, has been named chairman of the steering committee. Dr. Van Slyke and Dr. Marvin have stated that the meeting will be "the first national conference to bring together physicians, scientists, community service leaders and members of allied professions to formulate a program to combat and control the heart diseases."

Essay Contest.—The Mississippi Valley Medical Society will hold its Tenth Annual Essay Contest in 1950. The society will offer a cash prize of $100.00, a gold medal and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and of practical value to the general practitioner of medicine. Contestants must be members of the American Medical Association who are residents and citizens of the United States. All contributions shall be typewritten in English in manuscript form and submitted in five copies; they are not to exceed 5,000 words and must be received not later than May 1, 1950. Further details may be secured from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W. C. U. Building, Quincy, Ill.

Graduate and Postgraduate Courses at the University of California Medical School.—The graduate and postgraduate courses to be offered in 1950 at the University of California Medical School, Medical Extension, Medical Center, San Francisco, will include the following: Cardiology (Part II: Clinical Sciences as Applied to General Medicine), January 9 through May 22; Applied Therapeutics, January 3 through February 1; Forensic Medicine, February 6 through February 8; Internal Medicine and General Surgery, April 24 through April 28; Gastroenterology, August 28 through August 30; Evening Symposia in Medicine, Monday evenings, September 18 through December 4, and Microscopy and Photomicrography, twenty weeks beginning in January.

New Brazilian Journal of Psychiatry.—The *Journal brasileiro de psiquiatria* will constitute a continuation of the *Anais do Instituto de psiquiatria* of the University of Brazil and will publish the scientific, cultural and medico-social activities of that department of the University. Ordinarily, only previously unpublished, original articles will be used. These will contain summaries in English and in French. The journal will also accept symposiums, lectures, communications and résumés of interest to neuropsychiatrists. The chief editor is Prof. Maurício de Medeiros.

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